American Heart Journal

An international publication for the study of the circulation

VOLUME 96

JULY DECEMBER 1978

July 1978

American Heart Journa

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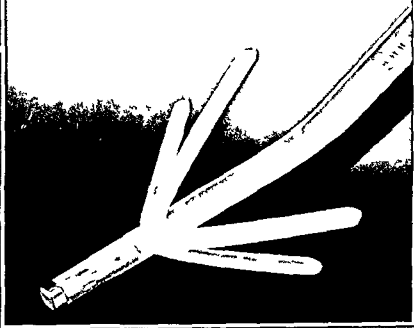
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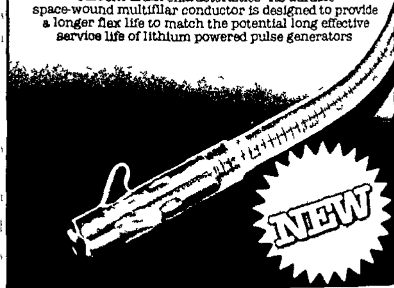
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Warnings

An ... tined lead

August 1978

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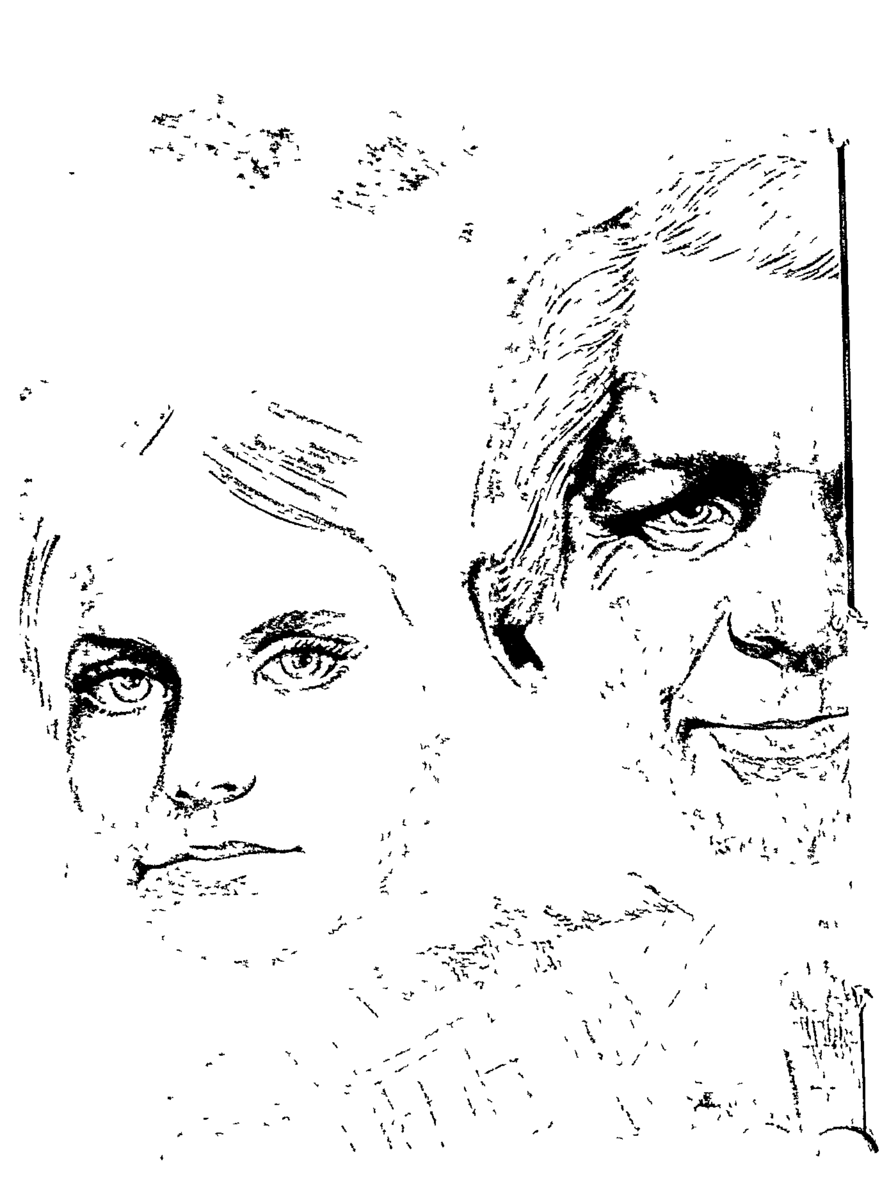
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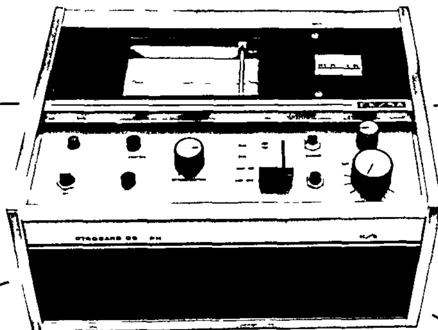
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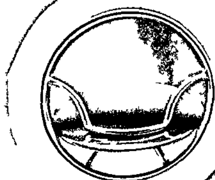
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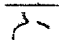
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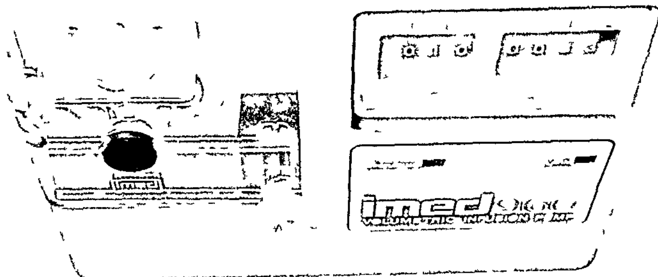
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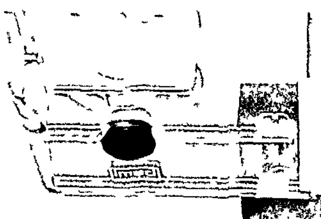
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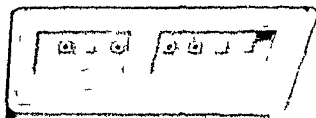
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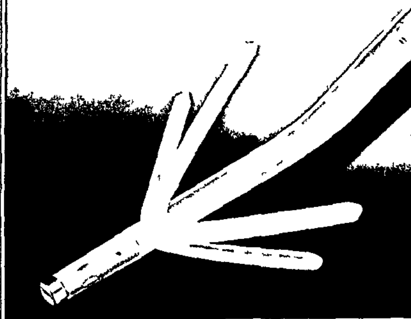
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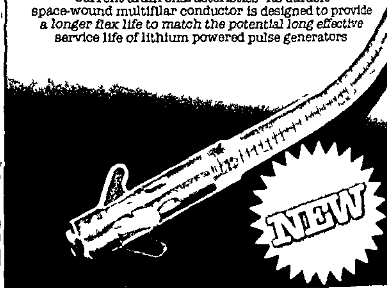
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PACING LEADS

MB

Intan

Medtronic implantable pacing leads are designed to be used wit.. Med ronic pulse g nerators as part of a ardiac pacing system (see product labeling for specific directions regarding app ications)

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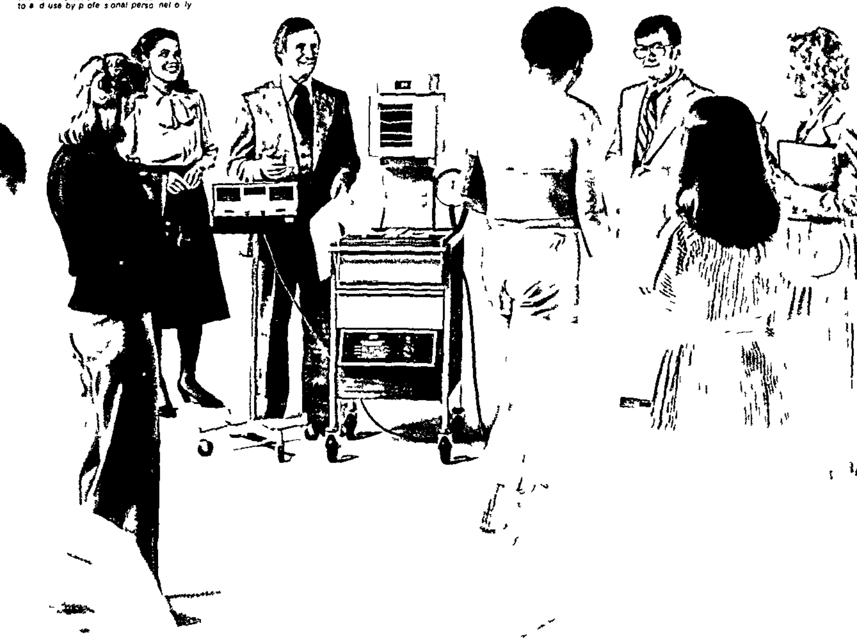
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American Heart Journal

July 1978 Volume 96 Number 1

Editorial

Surgical versus medical treatment in disease of the left main coronary artery

Ian M Graham MB MRCPI
Dublin, Ireland

To the outside observer the wholesale acceptance of coronary artery bypass grafting by the very country that scrupulously protects its citizens from the introduction of unproven new medications remains an extraordinary paradox That the reasons extend far beyond a simple consideration of what is good for the patient has been made abundantly clear by Preston s penetrating analysis Happily coronary artery surgery relieves angina pectoris in the majority of cases although the placebo effect of a thoracotomy is difficult to measure and unsuccessful operations may be associated with early symptomatic improvement[1] It is assumed but not proven that coronary artery bypass grafting is actually superior in terms of pain relief to discarded and obsolete procedures such as denervation induced pericarditis coronary sinus ligation or arterialization and internal mammary occlusion or implantation With the increasing tendency to offer operation to subjects with mild or even no symptoms the need to know whether this major procedure with its attendant morbidity and mortality actually prolongs life becomes ever more urgent

If coronary artery surgery prolongs life one might expect this to be most readily demonstrable in conditions which carry a poor prognosis and are readily amenable to surgical treatment such as left main coronary artery stenosis Many studies suggest that surgical treatment prolongs life in left main stenosis but how good is the evidence? One way to judge this is to draw up a list of design criteria and apply these to available studies Such a list might be

1 Precise diagnostic criteria
2 Prospective trial design
3 Randomly allocated concurrent controls
4 Stratified prognostic allocation
5 Predetermined starting times for observations of mortality and morbidity with details of the method of handling patients who die before surgery
6 Statement of the nature of the comparison is surgery being compared with no haphazard or optimal medical treatment?
7 Statement of medical treatment given to surgical patients before and after operation
8 Adequate sample size and duration of follow up

If one applies these criteria to five of the studies frequently quoted in reviews of surgical treatment of left main stem stenosis [illegible] the results are interesting (see Table I) Although we have written previously about one of these publications this table is not intended as a criticism of the papers themselves which are mostly carefully written observational studies It is however a vigorous criticism of those who quote such

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Received for publication March 9 1978
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significant left main lesions Circulation 54 (Suppl III) 3 107 1976

12 Murphy M L Hultgren H N Detre K Thomsen J and Takaro T Treatment of chronic stable angina A preliminary report of survival data of the randomized Veterans Administration cooperative study N Engl J Med 297 621 1977

13 Special correspondence A debate on coronary bypass N Engl J Med 297 1464 1977

14 Mulcahy R Hickey N and Graham I Natural history of post infarction angina pectoris (Abstr) Br Heart J 38 875 1976

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Table I Design criteria fulfilled by five studies of left main coronary artery disease

Reference	Design Criteria*								Total fulfilled
	1	2	3	4	5	6	7	8	
Lavine et al 1972	+	–	–	–	–	–	–	–	1
Demots et al 1975	+	–	–	+	–	–	–	–	2
Cohen and Gorlin 1975	+	–	–	–	–	–	–	–	1
McConahay et al 1976	+	–	–	–	–	–	–	–	1
Oberman et al 1976	+	–	–	–	–	+	–	–	2

See text paragraph 2 for explanation of design criteria

studies as if they were controlled trials proving the benefits of surgery They are not They may provide suggestive evidence indicating the need for a properly designed prospective study, but they cannot provide proof of the benefits or otherwise of surgical treatment Fortunately, the VA study[11 1] approaches more closely to the ideal and suggests that coronary artery bypass grafting prolongs life in the small sub group of symptomatic patients with left main stenosis poor left ventricular function, and disease of the right coronary artery This study has generated lively criticism,[13] some scientific and some clearly prejudiced Despite possible difficulties with randomization, a relatively high surgical mortality rate and the problems of coping with the 17 per cent of patients who received surgical treatment after starting in the medical group it must be stressed that this study is infinitely superior in design to anything which preceded it It is interesting to read surgical enthusiasts, who presumably have justified their commitment to surgical treatment on the basis of inadequate earlier studies protesting against the first attempt at a truly scientific experiment

A particular problem with most studies of the surgical treatment of left main stenosis is the lack of information about medical treatment given to either ' medically or surgically treated patients With aggressive risk factor modification and exercise programs the great majority of angina subjects can be managed satisfactorily [14] There is increasing evidence that subjects with proven coronary disease who stop smoking live longer than those who continue [15 16] The place of beta blockade remains controversial although some believe that it prolongs life, at least after myocardial infarction [17] There is a suggestion that anti hypertensive treatment postpones the development of overt coronary heart disease [18]

These studies are every bit as open to criticism as the quoted studies of coronary artery surgery, and do not refer specifically to left main stenosis which may be resistant to medical treatment If some or all of these findings are correct, however, there are important implications Trials of surgical treatment should include full details of medical treatment given to all groups of patients More importantly, rehabilitation and risk factor modification are free from morbidity and mortality and carry substantial additional health benefits

It is the author's belief that the time for rationalization (in the literal sense) of research into the treatment of coronary artery disease is long overdue Massive observational studies of surgical treatment are unlikely to yield useful information, but selective controlled studies will Too little is known about medical treatments which are promising, risk free, and logical

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Clinical communications

The error in indirect blood pressure measurement with the incorrect size of cuff

L A Geddes, M E, Ph D
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When the auscultatory (Korotkoff) method is used to measure blood pressure indirectly the accuracy is dependent on many factors the most important of which is the relationship of the width of the bladder in the cuff to the size of the member to which it is applied Cuff width is that dimension measured along the member, Fig 1 illustrates the terminology applied to blood pressure cuffs and presents a listing of the sizes presently available The aspect ratio (length to width) of most of these cuffs is about two to one The cuff width for human application has been specified by several cardiology groups[1-13] The most recent of these reports specified the correct cuff width as 20 per cent wider than the diameter of the arm Because arm diameter is difficult to measure accurately, this recommendation can be restated in terms of the arm circumference as follows cuff width should be $1.2/\pi = 0.382$ or about 40 per cent of the arm circumference This means that for a typical adult subject with a 30 cm arm, the cuff width should be 12 cm In the most recent[3] recommendations for cuff width it is stated that a cuff of 12 to 14 cm is adequate for the 30 cm adult arm The length of the bladder is such that it should half encircle the arm

It is well known by pediatricians that the measurement of blood pressure in children[4-8] requires that special attention be given to use of the correct cuff width in relation to the size of the member to which it is applied The use of a cuff that is too narrow provides falsely high, and the use of a cuff that is too wide provides falsely low values for indirect blood pressure Similarly in adult subjects it has been found[9-16] that the standard 12 cm wide cuff gives falsely high values for pressure when applied to large arms In fact, Orma and associates[13] described the situation as "cuff hypertension" It has been shown by Trout and colleagues[1] and by King and co workers[15] that by increasing the arm circumference by wrapping with cotton or sponge rubber falsely high values for indirect pressure are obtained Moreover Neussel and collaborators[17] have shown that the loose application of a standard cuff to the adult arm provides a falsely high value for indirect blood pressure

To reduce the error encountered when a standard cuff is applied to a large arm several investigations[13, 15, 18-20] have advocated the use of a longer, rather than a wider bladder in the cuff They reasoned that a long bladder would allow better transmission of the pressure in the bladder to the underlying artery However widespread support for this suggestion has not been forthcoming At present the length of the bladder is such that it encompasses about one half of the member circumference

From all of these reports it is clear that the width of the cuff in relation to the circumference of the member to which it is applied, importantly affects the values obtained for indirect blood pressure However there are few reports which specify the magnitude of the error to be expected when the incorrect cuff size is used either because the correct size is unavailable or because of a lack of knowledge of the correct size This paper

From the Biomedical Engineering Center Purdue University West Lafayette Ind

Supported by grant HL 18947 01 National Heart Lung and Blood Institute Bethesda Md

Received for publication Apr 26 1977

Accepted for publication Dec 19 1977

Reprint requests L A Geddes Ph D Director Biomedical Engineering Center Purdue University Institute for Interdisciplinary Engineering Studies West Lafayette Ind 47907

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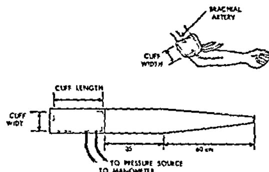
presents data which illustrates the amount of error to be expected when the cuff width departs from the optimum which is recommended to be 40 per cent of the circumference of the member to which it is applied

Methods and materials

To illustrate the order of error to be expected with cuffs which are too small and too large blood pressure was measured indirectly in a group of 52 healthy adult subjects using three standard cuffs (9 12 and 18 cm wide) applied to the upper arm The arms ranged from 21 5 to 36 cm in circumference Resting blood pressure was measured with each of the three cuffs using the auscultatory method During deflation of the cuff (at the rate of about 3 mm Hg per heart beat) the first sound (Phase I) heard with a stethoscope placed at the antecubital fossa indicated systolic pressure The cessation of sound (Phase V) signaled diastolic pressure In order to illustrate the effect of cuff width on indirect blood pressure readings the systolic and diastolic pressures obtained on each subject with the 12 cm cuff were taken as reference pressures In almost all cases it was found that this width was very nearly 40 per cent of the arm circumference The systolic and diastolic pressures obtained with the 9 and 18 cm cuffs were expressed as ratios of the systolic and diastolic reference pressures These ratios were then plotted versus the ratio of arm circumference to cuff width A linear regression line was determined for the data points for systolic diastolic and the combined pressures A previous study showed that there exists a hyperbolic correlation between the indirectly measured pressure and the ratio of cuff width to arm circumference A consequence of this fact is that there is a linear relationship between indirect pressure and the ratio of arm circumference to cuff width

Results

Fig 2 presents the values for the ratio of measured pressure to the reference pressure (12 cm cuff) versus the ratio of arm circumference to cuff width for systolic and diastolic pressures Fig 3 presents the distribution of ratios for arm circumference to cuff width for the three cuff widths applied to the 52 subjects Note that for both systolic and diastolic pressures the use of cuff that is too narrow (i e arm to cuff ratio greater than 2 48) resulted in a higher indirect



CUFF DESIGNATION	WIDTH (cm)	LENGTH (cm)
Newborn	2 3	6 0
	2 5	5 0
	3 0	6 8
	3 5	10 5
	3 7	7 6
I fant	4 5	11 5
	5 6	11 6
Child	8 3	15 7
	9 4	21 3
Ad lt	11 9	21 9
	12 4	25 9
La ge Adult	15 2	32 1
	15 5	31 3
Thigh	18 0	36 0
	18 6	40 2

Fig 1 The *meaning* of cuff width and length and the cuff sizes presently available

pressure Similarly with a cuff that was too wide (i e arm to cuff ratio less than 2 48) the measured pressure was lower An arm circumference to cuff width ratio of 2 48 is the same as a cuff width to arm circumference ratio of 0 403

Discussion

Of considerable importance in interpreting the data is Fig 3 which shows the histograms for the ratio of arm circumference to cuff width among the 52 subjects For the 12 cm cuff the mean ratio of arm circumference to cuff width was 2 30 The reciprocal of this value is 0 435 which is very close to the 0 4 value recommended as optimum for obtaining accurate indirect blood pressure values It is not coincidental that this group of subjects possessed arms which provided this value For the 9 cm cuff the mean value for the ratio of arm circumference to cuff width was 3 02 which corresponds to a cuff width to arm circumference ratio of 0 33 This cuff is therefore too narrow for these subjects and provided a combined indirect pressure reading of 5 7 per cent above the reference value obtained with the 12

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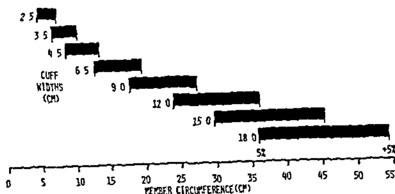


Fig 4 This illustration shows the error expected for indirect blood pressure when the cuff width deviates from a value which is 40 per cent of the member circumference The ends of each bar represent a +5 per cent *(right)* and a −5 per cent *(left)* error in indirect blood pressure measurement

was applied to the arms of human subjects and the readings obtained were compared either with direct arterial pressure or with the values obtained relative to one size of cuff Accordingly the data presented in the papers by Erlanger Robinow and colleagues[3] Day Ragan and Bordley[6] Trout and associates[7] Simpson and co workers[8] King[3] Kvols and collaborators[9] and Burch and Shewey[22] were plotted in the manner shown in Fig 2 to represent the ratio of indirect to direct (or reference 12 cm cuff) pressure versus the ratio of arm circumference to cuff width Linear least squares lines were obtained for each set of data From the slope of this relationship is revealed the percentage error expected when the cuff width deviates from 40 per cent of the arm circumference In those papers where the least squares line did not pass through the ratio of cuff width to arm circumference equal to 0 4 a proportional adjustment was made without altering the slope of the regression line Thus the data from all of these reports were represented by straight lines passing through the 0 4 point on the axis representing arm circumference to cuff width ratio Then the values for the ratio of cuff width to arm circumference corresponding to a plus five and minus five per cent error were identified for each subject. Using these minimum and maximum cuff to arm ratios the ranges of member circumference for a ±5 per cent error in indirect blood pressure measurement (with respect to the AHA recommended cuff size) were calculated for the 2 5 3 5 4 5 6 5 9 12 15 and 18 cm cuffs Fig 4 presents the result of this analysis and shows the cuff widths that are appropriate for members ranging from 5 to 55 cm The cuff widths chosen represent those that have been described in the literature or sizes that are presently available The illustration points out that use of a cuff that is narrower than the recommended width results in an overestimation of pressure and the use of a cuff that is wider than that recommended results in an underestimation of pressure

Cuff widths corresponding to the centers of the black bars in Fig 4 represent a cuff width to arm circumference ratio of 0 4 The extremities of the bars represent the extreme value of member circumference which will produce a ±5 per cent error in measured pressure for a given cuff

In order to relate the information obtained in this study to present practice we calculated the range of arm circumference for each of the cuffs provided by the two largest manufacturers of spygmomanometers The limits of arm circumference were based on obtaining a ±5 per cent error in blood pressure measurement It was found that one manufacturer provides cuffs that are based on the American Heart Association criterion i e optimum cuff width equals 40 per cent of the member circumference The limit marks on the cuff provided by this manufacturer are in good agreement with the ±5 per cent error in blood pressure found in this study with the exception of the thigh cuff which indicates that it is applicable to larger members than we would recommend It was found that the other manufacturer provided cuffs which were centered about a ratio for cuff width to member circumference equal to 0 345 i e slightly less than that recommended by the AHA However for all cuffs the range of arm circumference limits coincided very well with the ±5 per cent criterion presented in this paper

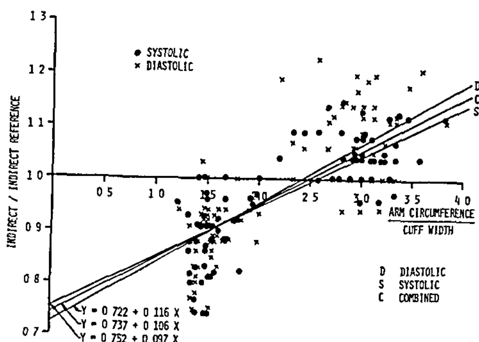


Fig 2 The ratio of measured indirect pressure to reference (12 cm cuff) pressure versus the ratio of arm circumference to cuff width for the 52 subjects

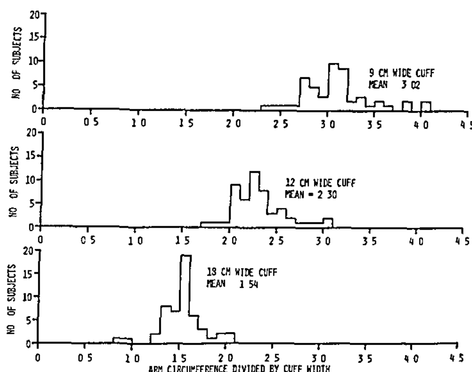


Fig 3 Distribution of the ratio of arm circumference to cuff width for the 52 subjects

cm cuff Likewise, the mean ratio of arm circumference to cuff width for the 18 cm cuff applied to the subject was 1 54 The reciprocal of this figure is 0 67, i e the cuff width was 67 per cent of the arm circumference This cuff was therefore too wide and provided combined indirect pressure readings which were 10 per cent below the reference values obtained with the 12 cm cuff

The American Heart Association recommends that the cuff width should be 1 2 times the arm diameter, i e 40 per cent of the arm circumference However, it is not always possible to select a cuff width which is exactly 40 per cent of the arm circumference In practice the cuff is usually narrower or wider than this optimum value The magnitude of error to be expected with a cuff width that is not optimal can be estimated from the type of relationship presented in Fig 2

In addition in the published literature there are several reports in which a range of cuff widths

Distinctive echocardiographic pattern of posterior wall endocardial motion in aortic stenosis*

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In aortic stenosis (AS) the prolonged ejection time[1] and slowly rising arterial pressure pulse [3] reflect the abnormal manner in which blood is ejected from the left ventricle Thus a slow prolonged rise in the arterial pulse (which primarily results from a slow volume rise in the proximal arterial tree) might be expected to produce a slow prolonged decrease in ventricular volume provided no shunt or mitral regurgitation is present In this regard we have noted a characteristic saw toothed pattern of posterior wall endocardial motion on M mode echocardiography in aortic stenosis in which the left ventricular (LV) posterior wall endocardium has a nearly constant systolic rise lasting until the abrupt onset of its posterior motion (see Fig 1) This contrasts with the normal pattern in which despite distortion by movement of the left ventricle as a whole during late systole and early diastole the endocardial rise gradually plateaus in systole more clearly reflecting the rapid and slow phases of LV ejection

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This work was supported in part by United States Public Health Service Training Grant HL-056 3 and United Sates Public Health Service SCOR in Ischemic Heart Disease HL-1 648 and RCDA HL 70-132.

Received for publication May 19 1977

Accepted for publication Aug. 31 1977

Reprint requests Dr Harold Brooks, The Medical College of Wisconsin Milwaukee County Medical Complex 8700 West Wisconsin Avenue Milwaukee Wisc 53226.

*Presented in part at the 26th Annual Session of the American College of Cardiology Las Vegas, Nevada March, 1977

0002-8703/ 8/0196-0009$00.80/0 © 19 8 The C V Mosby Co

In this study we have examined the endocardial motion in four distinct groups of patients those with aortic stenosis those with severe hypertension those with coronary artery disease with aortic ejection murmurs but no aortic valve gradient (designated herein as aortic sclerosis —A Scl) and those with no demonstrable heart disease The patients with aortic stenosis and hypertension were matched in terms of systolic pressure load and degree of left ventricular hypertrophy The study was also designed to determine whether the abnormal pattern could be reproducibly recognized by different observers thus providing a practical non invasive marker in the assessment of aortic stenosis

Methods

Patient populations *Group A* consisted of 33 of 41 consecutive patients with hemodynamically proved aortic stenosis who were studied at our Echocardiography laboratories between June 1973 and July 1976 Of the 41 patients with AS 33 had suitable M mode echocardiographs and cardiac catheterization performed within 72 hours during the 3 year period Four patients (12 per cent) had technically unsuitable recordings and four did not have echocardiography performed Patients with other valvular lesions were included in the study (see Table I) Two cases (No 4 and No 12) were in atrial fibrillation the remainder were in sinus rhythm at the time of study Patient age ranged from 23 to 72 years with a mean of 56 years Group A was divided into patients with valve areas < 1 cm^2 (AS < 1 cm^2)

Conclusion

The data in this report, and those presented in the published literature, show that the use of a cuff that is too narrow overestimates and one that is too wide underestimates indirect blood pressure A cuff width to arm circumference ratio of 0 34 overestimates blood pressure by about 5 per cent, a cuff width to arm circumference ratio of 0 50 underestimates blood pressure by 5 per cent For the same degree of mismatch, the error is greater when the cuff width is narrower rather than larger

Summary

This paper shows the error to be expected when blood pressure is measured indirectly with a cuff that is too wide or too narrow for the member to which it is applied A cuff that is too narrow overestimates and a cuff that is too wide underestimates blood pressure

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This wo k w s supported in part by U ted States Public Health Service Tra ning Grant HL-056 3 and United S tes Public Health Service SCOR in Isch mic Heart Disease HL-17648 and RCDA HL 70-132

Rece ed f r publication May 19 1977

Accepted fo p bli t o Aug 31 1977

Reprint req ests Dr Harold Brooks, The Medi al Coll ge of Wiscon-sin Milw kee C unty Medical Complex 8700 West Wisc nsin A enue Milwaukee Wisc. 53226

*Presented in part at th 26th Ann al Session of the American College of C rdi logy Las Vegas N ada March, 1977

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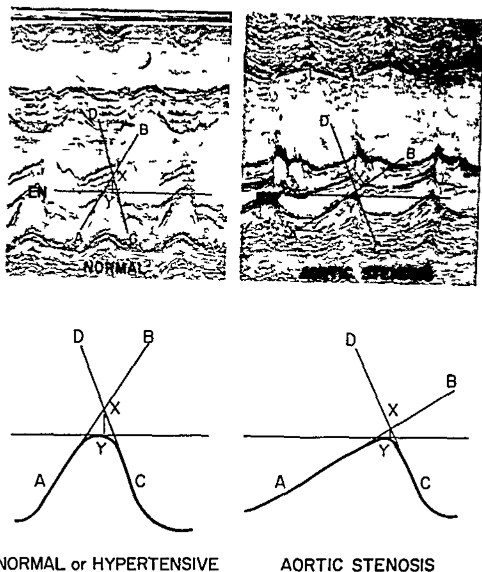


Fig 1 Diagram comparing the typical posterior LV endocardial motion in hypertensive patients and normals with that in aortic stenosis The method of calculating the value XY is illustrated

and those with areas greater than or equal to 1 cm² (AS ≥ 1 cm²)

Group B consisted of 33 of 52 consecutive patients with severe untreated hypertension who had suitable M mode echocardiograms recorded in our laboratories between July, 1974 and November, 1976 Of the 52 patients 12 had normal posterior wall thickness (less than or equal to 11 mm) on echocardiography Of the remaining 40 33 were selected without knowledge of the posterior wall appearance to match values of the ratio diastolic LV posterior wall thickness (hd) LV internal diameter ratio (Dd), with those of the 33 patients in Group A, thus providing a basis for comparison of the pressure loads in both groups The validity of this echocardiographic index has previously been described by Grossman and colleagues[5]

Mean hd Dd was 0 342 ± 0 014 in Group A and 0 343 ± 0 013 in Group B Mean peak systolic pressures were 188 ± 5 9 mm Hg in Group A (intraventricular) and 181 ± 4 4 mm Hg in Group B (arm cuff) Thus patients in both Groups A and B had a similar mean systolic pressure load and degree of left ventricular hypertrophy Mean age of the 33 patients was 42 years with a range of 29 to 62 years None of the patients had evidence of associated valvular or ischemic heart disease and none had evidence of left ventricular failure

Group C comprised 12 randomly selected patients with Grade 2 3/6 harsh ejection murmurs and who on diagnostic cardiac catheterization had minimal (< 10 mm Hg) or no transaortic valvular peak systolic gradients and normal cardiac outputs Most of these patients were elderly (mean age, 61 years) and had coronary artery disease with angiographically demonstrated coronary narrowings of ≥ 75 per cent lumen diameter in one or more arteries Such

Table I Clinical echocardiographic and hemodynamic data in 33 patients with aortic stenosis

					Echocardiographic data									*Hemodynamic data*			
Pt	*Age/ sex*	*BP (mm Hg)*	*Other lesions*	*LVF*	*Dd (cm)*	*Ds (cm)*	*hd (cm)*	*hs (cm)*	*Sd (cm)*	*hd/ Dd*	*Mean XY (cm)*	*Abn En*	*FS*	*PSGr (mm Hg)*	*AVA (cm)*	*LVS/ LVEDP*	*LVSC*
1	54/F	80/60	MS3+ MR1+ AR1+	–	35	25	1.5	18	18	043	007	+	29	80	06	160/10	–
2	51/M	125/65	AR2+	–	47	36	16	20	1.9	034	00	+	23	100	06	225/40	–
3	72/M	190/60	AR3+	–	61	45	18	24	22	029	032	–	26	10	19	200/18	–
4	43/F	98/65	AR2+ MR2+ TR1+	–	40	2.2	11	17	11	027	040	–	4ɔ	30	11	130/11	–
5	45/M	140/70	MS1+ AR3+	–	58	38	11	2.2	11	019	070	–	34	10	21	140/10	–
6	50/F	140/60	AR3+ MS1+	–	61	39	17	30	20	0?8	02?	+	36	30	17	180/11	–
7	70/F	150/90	MR1+	–	34	22	15	21	16	044	007	+	35	70	0ɔ	224/22	–
8	38/F	130/90	MS2+	–	42	28	15	21	14	036	030	–	33	40	1.2	170/12	–
9	70/F	130/60	AR?+ MS2+	+	50	40	1.3	1.8	16	0.26	003	+	20	50	06	175/18	–
10	5?/F	150/80	AR2+ MS2+ TS1+	–	50	33	14	22	14	028	027	–	34	10	2.2	190/06	–
11	65/F	130/90		–	33	21	1ɔ	18	17	045	020	+	36	90	06	230/1?	–
12	63/M	110/60	AR2+ MS2+	+	6.3	50	13	2.0	14	021	010	+	21	30	1.5	140/15	+
13	60/M	100/60		–	42	28	13	18	1.3	031	027	+	33	25	14	170/25	–
14	68/F	140/70		–	50	38	1?	2.2	16	034	013	+	24	75	09	2?0/20	–
15	23/M	140/70	MS1+ AR2+	–	36	2.5	18	2.5	16	050	007	+	30	55	07	200/1?	–
16	52/F	150/80	AR1+	–	42	25	16	2.1	2.3	038	007	+	40	80	06	240/08	–
17	59/M	130/60	AR2+	–	57	40	14	18	13	025	023	+	30	15	18	145/16	–
18	46/M	110/ 5	†	–	50	40	14	16	13	0?8	010	+	20	30	1.2	142/14	–
19	26/M	110/ 0		–	36	18	13	20	15	036	013	+	50	50	10	160/18	–
20	61/M	110/70		–	40	30	1.5	2.2	15	0.37	010	+	2ɔ	55	08	230/32	–
?1	66/M	130/80	MS1+	–	3.8	31	17	21	1.8	045	007	+	18	70	05	200/30	–
2?	53/M	1?0/90	AR2+	+	51	40	14	2.0	14	0.27	0.20	+	21	40	04	180/40	–
23	65/F	100/ɔ5		–	4.5	35	1.5	20	16	033	010	+	22		06		–
?4	48/F	105 80		–	42	30	17	2.2	16	040	010	+	29	95	05	200/20	–
25	58/M	105/90	MS?+ MR1+ AR1+	–	42	30	14	21	14	033	010	+	29	42	08	18?/15	–
?6	55/M	105/85		–	42	31	18	2.3	20	042	023	+	26	100	07	210/35	–
27	70/F	130/90	MR1+	–	46	32	19	2.1	17	041	0?8	+	30	90	08	230/22	–
28	66/F	130/80		+	40	30	17	2.6	17	04?	040	+	2ɔ	105	04	230/15	–
29	63/M	100/80		+	50	40	17	2.1	16	03?	010	+	20	110	025	2?0 45	+
30	65/M	130/90	AR1+	–	53	42	1.8	21	16	034	007	+	21	40	0ɔ	180/30	+
31	68/M	125/ɔ0		+	50	42	19	28	17	038	017	+	16	30	11	17ɔ/18	–
32	33/F	120/90	AR?+	–	51	32	11	15	11	02?	065	–	37	20	13	14ɔ/10	–
33	62/M	120/90		–	40	32	17	20	17	042	017	+	20		06		+

Abbreviations BP = blood pressure d termined by arm cuff method MS = mitral stenosis MR = mitral regurgitation AR = aort c regurgitation PSGr = peak systoli gradient AVA = aort valve are LVS = l ft ventricul r systoli pressure LVEDP = left ventricular end diastolic pressure LVSC = left tricular segm tal ch ng Pt = p tient M = male F = fem le

= estim ted at surg ry

† = aortic p osthesis.

Me n XY = mean of the measurem nts for XY by the 3 observers Abn En = abnormal endocardial ppearance as assessed by a majority of observati ns of the 3 observers LVF = left ventricular fail re Ld = posterior wall thickness in diastole Ls = posterior wall thickness in systole Dd = left ventricular internal diastolic dim nsion Ds = left ventricular internal systolic dimension

patients were designated as having aortic sclero sis Four of these patients had a history of previous anterior myocardial infarction and one previous inferior infarction

Group D consisted of 30 patients selected as normal controls All had a negative history for heart disease normal cardiovascular findings and normal electrocardiograms blood pressure was less than or equal to 140/90 mm Hg Mean patient age was 53 years with a range of 16 to 85 years

Echocardiographic technique Echocardio grams were performed using a Unirad echocardio graphic ultrasonoscope and strip chart recorder

Table II Analysis of posterior wall endocardial motion by 3 independent observers

	PW endocardial pattern—inspection alone							*Assessment by distance XY*						
	Observer 1		*Observer 2*		*Observer 3*			*Observer 1*		*Observer 2*		*Observer 3*		
	AbnEn	*Nl*	*AbnEn*	*Nl*	*AbnEn*	*Nl*	*Agr %*	*AbnEn*	*Nl*	*AbnEn*	*Nl*	*AbnEn*	*Nl*	*Agr %*
AS < 1 cm²	19	1	16	4	20	0	84	19	1	20	0	20	0	97
AS ≥ 1 cm²	8	5	8	5	5	8	67	9	4	9	4	8	5	72
HT	4	29	3	30	2	31	90	3	30	3	30	2	31	86

Abbreviations PW = posterior wall AbnEn = abnormal posterior wall endocardial appearance (see text) Nl = normal posterior wall endocardial appearance Agr % = interobserver agreement rate AS < 1 cm = aortic stenosis valve area less than 1 cm² AS ≥ 1 cm = aortic stenosis valve area greater than 1 cm HT = hypertensive patients

A 2 25 MHz ultrasound transducer with a pulse frequency of 1538/sec was utilized The recordings and standard measurements were performed as described by Feigenbaum[6] The patients were studied in the supine or left lateral position Particular care was taken to clearly delineate posterior wall endocardium and epicardium Posterior wall thickness measurements were taken at the peak of the R wave, from the anterior edge of endocardium to the anterior edge of the epicardium Fractional shortening (FS) was calculated using the formula

$$FS = \frac{Dd - Ds}{Dd}$$

where *Dd* = LV internal dimension in diastole and *Ds* = LV internal dimension in systole All echocardiographic measurements were made without knowledge of the catheterization findings

Hemodynamic assessment Full right and left heart catheterization was performed in all patients with significant aortic murmurs and/or other findings suggesting significant aortic valve disease This comprised all of groups A and C Aortic valve area was calculated by the Gorlin hydraulic formula[7] Valve area was estimated at surgery in two of the patients in whom the aortic valve could not be crossed LV failure, defined by Standard Clinical Criteria and/or an LV ejection fraction at catheterization of less than 45 per cent was present in 6 out of 33 cases Coronary arteriography was performed in 34 of the 45 patients Significant arterial lesions were present in 18 cases (six with aortic stenosis and all 12 of the aortic 'sclerotic group) Nine had segmental abnormalities on left ventricular angiography, including four patients with aortic stenosis and five with aortic sclerosis Segmental abnormalities were not present in cases without significant coronary artery disease In the group with aortic valve area < 1 cm², nine patients had pure aortic stenosis and 11 had associated lesions (including eight with aortic regurgitation)

Posterior wall endocardial motion assessment To evaluate the ability to recognize the characteristic saw tooth pattern in an unbiased fashion echocardiograms from the aortic stenotic (Group A) and hypertensive (Group B) patients showing only the left ventricle were mixed and independently analyzed by three physicians unaware of the diagnoses or catheterization findings In this way assessment could not be biased by the presence of increased aortic root echoes (present in 29 out of 33 cases of AS) Assessment in Groups C and D could not be similarly blinded as the normal wall thickness in these groups allowed immediate differentiation from the group with aortic stenosis Analysis was then made in the following ways

1 To assess whether the appearance could be recognized by visual impression alone the three observers graded appearances in Groups A and B as either (a) positive if the abnormal motion was definitely or probably present or (b) negative if it was either definitely or probably not present Interobserver reproducibility and degree of prediction for aortic stenosis were assessed

2 In an attempt to evaluate endocardial motion in a simple yet objective way the recordings in Groups A and B were again mixed and lines were drawn tangential to the endocardium at the point of its maximal rate of rise and at its maximal rate of fall (lines *AB* and *DC* in Fig 1) The vertical distance between the point of intersection (*X*) of these lines and a line joining the peaks of the endocardium was measured (*XY* in Fig 1) and corrected for scale expansion Each observation involved averaging at least two

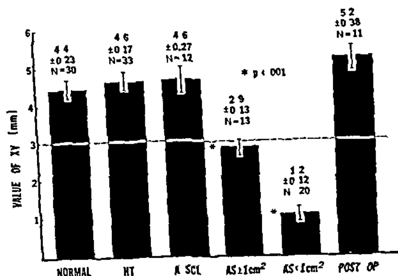


Fig 2 Values (means with standard errors) of XY in normals, hypertensive patients (HT) aortic "sclerosis" (*A Scl*) and aortic stenosis with (a) valve area greater than or equal to 1 cm (AS ≥ 1 cm²) (b) valve area less than 1 cm (AS < 1 cm) and (c) after aortic valve replacement (*post op*) * Paired t test comparing AS with HT Note decreasing values for XY with increasing severity of stenosis A value of XY of 3 mm or less can be seen to differentiate aortic stenotic patients from the other groups

measurements of XY A low value of XY was expected if the endocardium had the abnormal saw toothed appearance (see Fig 1) These results were again assessed for ability to predict AS and for agreement in predictions between the observers

3 The pattern of endocardial motion in the records from Group C (patients with aortic sclerosis) and Group D (age matched normals) were assessed as above by one observer The effect of heart rate on mild exercise (heart rate 110 to 120) was assessed in 10 of the normal patients To assess the possible effect of changing paper speed upon the abnormal endocardial appearance recordings were made at various speeds in five of the normal patients

4 Endocardial motion was assessed at varying intervals ranging from 3 days to 18 months postoperatively in 11 of the 15 patients who underwent aortic valve replacement

5 Serial LV dimensions were recorded at 15 msec intervals in selected aortic stenotic (valve areas < 1 cm) and hypertensive patients thus allowing graphs of LV dimension against time to be drawn A sonic pen digitizer and a computer were utilized in measurement and analysis of the dimension changes The time (T) between that point in the latter part of ejection at which shortening in LV internal dimension had fallen to half its maximal rate to the point at which end systole occurred was measured in 13 patients with significant aortic stenosis and 13 patients with hypertension who were selected without knowledge of the posterior wall endocardial appearance on the basis of matching hd Dd ratio End systole was defined as the point at which the shortest LV dimension occurred This method of analysis of serial LV dimension was chosen to determine whether significant shortening in LV dimension (i e at half the maximal rate) was occurring at a relatively later stage in systole in aortic stenosis as suggested by the abnormal endocardial appearance The remaining seven patients with AS < 1 cm² could not be accurately analyzed because of segmental abnormalities (two cases) paradoxical septal motion (left bundle branch block type) (two cases) technical problems (two cases) and insufficiently clear left side of septum (one case)

Results

Ninety nine observations by both visual assessment and by calculation of XY were performed in the aortic stenotic and hypertensive groups (one by each of the three observers) In the other groups one observation per patient by both methods was performed

Assessment of endocardial motion by inspection alone The abnormal motion was assessed as being present in 55 out of 60 (92 per cent) of

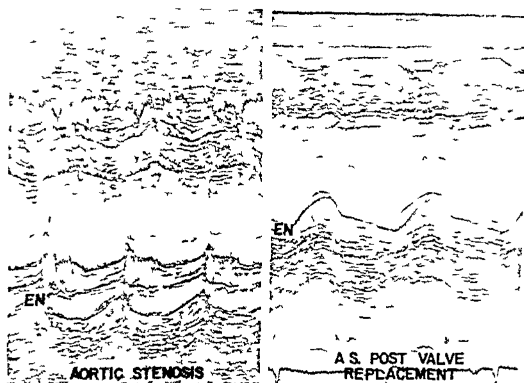


Fig 3 Preoperative and one year postoperative echocardiograms in a patient with severe aortic stenosis and moderate aortic regurgitation (Case No 2) Note that after aortic valve replacement the abnormal endocardial motion returned to the normal pattern

observations in AS with valve area < 1 cm and 21 out of 39 (54 per cent) with a valve area ≥ 1 cm² These compared to only 9 out of 99 (9 per cent) of hypertensives, 0 out of 12 (0 per cent) of the aortic sclerotic group, 1 out of 30 (3 per cent) of normals, and 1 out of 11 (9 per cent) of post aortic valve replacement cases Table II shows the breakdown of observations in Groups A and B by each observer When the observations were paired to assess interobserver agreement rate agreement in prediction was demonstrated in 84 per cent of predictions in AS < 1 cm², 67 per cent of predictions in AS ≥ 1 cm² and 90 per cent in the hypertensive patients

Assessment by use of Distance XY Fig 2 shows the mean values for XY in the different patient categories There was a highly significant statistical difference ($p < 001$) both between the mean values for XY in AS < 1 cm and AS ≥ 1 cm and between AS < 1 cm and hypertensive patients A value for XY of 3 0 mm or less was taken to indicate the presence of the abnormal motion, as this value best distinguished the group with AS < 1 cm² (see Fig 2) When assessed in this way the abnormal motion was present in 59 out of 60 observations (98 per cent) of AS < 1 cm² and 29 out of 39 (67 per cent) of AS ≥ 1 cm², contrasting with 8 out of 99 (8 per cent) of hypertensives 1 out of 12 (8 per cent) of the aortic sclerotic group, 5 out of 30 (17 per cent) of normals, and 1 out of 11 (17 per cent) of the post valve replacement group Interobserver agreement in prediction was found in 97 per cent of AS < 1 cm², 72 per cent of predictions in AS ≥ 1 cm² and 86 per cent in the hypertensive patients The poor interobserver agreement in predictions in the patients with AS ≥ 1 cm² reflected the mean value for XY in this group which was intermediate between AS < 1 cm and hypertensive patients

Mean fractional shortening was 28 per cent in the aortic stenotic group and 32 per cent in the hypertensive patients, the similar finding suggesting that over all LV dysfunction did not cause the abnormal motion The mean fractional shortening in the AS group was similar to that of reported adult patients with AS[10] Increasing heart rate in the 10 normal patients did not influence the value for XY significantly (mean XY = 0 42 cm) Changing paper speed did not influence the value of XY

Echocardiographic assessment following aortic valve replacement Fifteen of the 20 patients with aortic valve area < 1 cm underwent aortic valve replacement In 11 of these repeat tracings were obtained ranging from 3 days to 18 months postoperatively As noted above, in nearly all cases the endocardial pattern returned to normal

(including the study performed 3 days postoperatively) Fig 3 shows representative echocardiograms before and 18 months after valve replacement

Serial LV dimension study The mean value for T (the time between shortening at half maximal rate and end systole) was significantly decreased ($p < 005$) in the group with AS < 1 cm² as compared to the hypertensive group (37 msec compared to 97 msec) Thus shortening in LV dimension at half the maximal rate occurred much closer to end systole in the group with AS < 1 cm²

Discussion

This study clearly differentiates the posterior wall endocardial motion in patients with significant aortic stenosis from that in hypertensive aortic sclerotic and normal patients The change appears to be related to the aortic valve narrowing since similar degrees of hypertrophy and pressure load were present in the aortic stenotic and hypertensive groups Evidence for this conclusion is further corroborated by the fact that the abnormal motion disappeared after aortic valve replacement Age and generalized myocardial dysfunction were not considered causative since the abnormal motion was not usually present in the age matched normals and fractional shortening was similar in hypertensive and aortic stenotic patients In the 10 normal patients in whom heart rate was increased by exercise to rates varying from 110 to 120 per minute a shorter plateau in the endocardial motion was compensated by an expected increase in the AB and CD slopes secondary to increased rate of shortening and relaxation during exercise thus resulting in a normal mean value for XY Associated valve lesions also did not influence the characteristic saw tooth appearance Similar endocardial appearances are present in echocardiograms of aortic stenosis in the previous literature where the left ventricle is shown

M mode echocardiography provides an opportunity to examine posterior wall endocardial motion in great detail with its high sampling rate capabilities This motion to some extent reflects over all cardiac function in the absence of coronary artery disease [13] A localized cause for the abnormality was unlikely as significant coronary artery disease was present in only 6 out of 33 cases of aortic stenosis and posterior wall segmental abnormalities on LV angiography (that region likely to be visualized on M mode echocardiography) were present in only two cases Production of the abnormal posterior wall endocardial appearance by abnormal whole heart swing was also considered unlikely since the cases with aortic stenosis had no evidence of abnormal whole heart swing elsewhere in the left ventricle and since the endocardial changes were reflected in changes in over all LV dimension

It thus appears that the abnormal endocardial motion is a reflection of an over all change in the ejection pattern in aortic stenosis The resumption of the normal pattern following aortic valve replacement parallels the decrease in ejection time[1] and normalization of the carotid pulse character[2] usually seen after aortic valve replacement The appearance after valve replacement was identical to the normal pattern (see Fig 3) and thus unlikely to be caused either by abnormal heart swing or as compensatory to the abnormal septal motion seen after cardiac surgery (see Fig 3) where some residuum of the abnormal pattern would be expected

The value XY probably effectively differentiates the abnormal pattern because of the constancy of the endocardial rise in aortic stenosis until abrupt posterior endocardial motion occurs (which results in a saw toothed endocardial pattern) This appearance taken in conjunction with the serial dimension study suggests that shortening is occurring later in systole in aortic stenosis to compensate for diminished ejection in the early rapid ejection phase Diminished left ventricular compliance secondary to left ventricular hypertrophy lowers the DC slope this affects XY to a lesser degree however as evidenced by the normal values for XY in hypertensive patients whose LV hypertrophy and systolic loads were comparable to the aortic stenotic patients Despite the small values of XY involved the clear separation between the aortic stenotic and all other groups usually allowed confident characterization of the endocardial appearance In those normal cases where the value for XY was abnormal it is possible that an abnormal degree of anterior late systolic heart swing was responsible Values for XY were generally borderline in these cases (four of five cases classified as abnormal had values of XY = 3 mm)

The abnormal pattern is most helpful in the

diagnosis of significant aortic stenosis on M mode echocardiography, particularly in view of the high rate of detection of significant AS using the value XY As all of our patients with significant AS had a wall thickness of 13 mm or greater (see Table I), and wall motion was assessed as abnormal in nearly all of the observations we feel the absence of both features essentially excludes significant AS in the adult age group As has been noted by others, we found increasing degrees of wall thickness with more severe degrees of aortic stenosis[10 15] We strongly suspect significant aortic stenosis when the combination of the abnormal motion, a posterior wall thickness greater than 14 mm, normal or decreased LV size, and thickened ill defined aortic valve cusps are all demonstrated These guidelines are especially useful considering present difficulties in diagnosing aortic stenosis using M mode echocardiography[6 16], the sign being particularly helpful in aortic regurgitation where the association of aortic stenosis is sometimes difficult to determine, and in patients with aortic 'sclerosis' where aortic root echoes may be thickened and the carotid pulse misleading

Conclusion

Posterior wall endocardial motion was studied by M mode echocardiography in varying degrees of aortic stenosis documented at cardiac catheterization and compared to hypertensive patients with matched systolic loads and normal controls In 20 patients with valve area < 1 cm² a distinctive 'saw toothed pattern of motion consistent with the slowly rising arterial pulse of AS was seen (114 out of 120 observations) When the aortic valve area was ≥ 1 cm² the saw toothed pattern was seen less commonly (47 out of 78 observations, 13 patients) and was rarely seen (1 out of 24 observations 12 patients) with coronary artery disease aortic ejection murmurs but insignificant aortic valve gradients (aortic 'sclerosis) The abnormal pattern was seen in only 8 per cent of 33 hypertensive patients with hypertrophy and pressure loads comparable to the 33 aortic stenosis patients and 10 per cent of 30 age matched normals Following aortic valve replacement the pattern reverted to normal in nine of 11 patients restudied suggesting that the phenomenon is a dynamic response to fixed outflow obstruction rather than a permanent anatomic (mural) abnormality With echocardiographic evidence of left ventricular hypertrophy associated with typical aortic root abnormalities, this characteristic pattern is a most helpful sign in the diagnosis of aortic stenosis

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Unusual complications of coronary bypass surgery

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Since the advent of coronary bypass surgery each year an increasing number of patients are subjected to this procedure with good results[1] Reported complications of saphenous vein bypass surgery have included pulmonary emboli and myocardial infarction or postoperative appearance of pathologic new Q waves associated at times with deterioration of the left ventricular function due to closure of the graft or trauma caused by left ventricular apical venting[3, 4] A few case reports described post bypass appearance of new systolic[5] or continuous murmurs due to normal or stenosed graft [7] or to anastomoses of the graft to coronary vein[8] and in one case to a coronary ateriovenous fistula[8] Other complications include false aneurysm of the vein graft[9] intimal tear with or without dissecting aneurysm of the aorta [0] and transmyocardial left to right shunt [2]

Here we report five cases three of whom developed post bypass apical thrombus one developed a moderate degree of new mitral regurgitation and in the other patient there was stagnation of angiographic contrast material around the distal anastomatic site To our knowledge these complications have not been described

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Received for publication May 23 1977
Accepted for publication Aug 19 1977

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Material

Between December 1969 and February 1977, 900 patients underwent saphenous veing bypass surgery Postoperative angiograms were performed in 585 patients Among these patients in three (Cases 1 2 and 3) postoperative angiograms showed new apical thrombi which were not present prior to surgery In one patient (Case 4) there was stagnation of angiographic material around the distal anastomatic site of the vein graft to the diagonal branch of the left anterior descending artery The fifth patient (Case 5) developed new mitral regurgitation

Operative Technique

All patients had reversed saphenous vein aorto coronary bypass utilizing total cardiopulmonary support Priming solution was 5 per cent dextrose in one third normal saline Flow rates were 40 to 55 ml /Kg using a bubble oxygenerator with mean arterial pressures of at least 50 mm Hg The left ventricle was vented through the right superior pulmonary vein None of these patients had apical venting Moderate hypothermia was achieved by cooling the patient to 32° C After total cardiopulmonary bypass the ventricle was occasionally electrically defibrillated and aorta was intermittently clamped for the distal anastomoses

Case 1

A 65 year old white female who had documented anterior wall myocardial infarction 14 months and double saphenous vein bypass surgery four months earlier was admitted to the hospital for the second time in August 1976 with recurrent

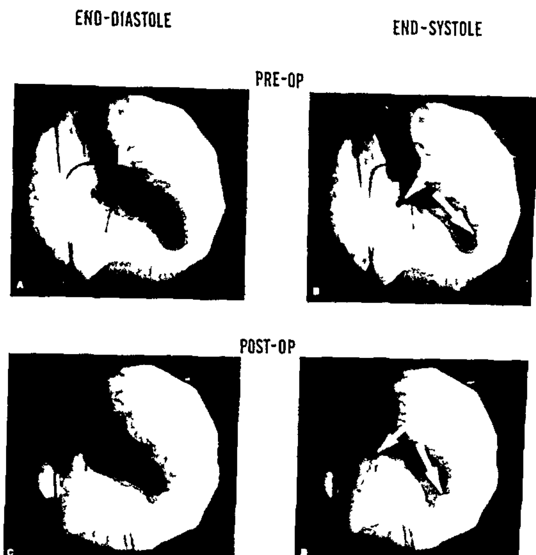


Fig 1 Pre and postoperative left ventricular angiograms of Case No 1 as viewed in the right anterior oblique projection Prior to surgery (*Pre op*) she had prolapsed mitral valve and apical akinesia (*arrow in end diastole*) postoperatively (*post op*) not only prolapsed mitral valve remained unchanged (*upper arrow*) but the patient also developed apical thrombus (*lower arrow*)

angina pectoris On her first admission in April 1976 she gave a history of typical angina pectoris initially on exertion then at rest and nocturnally for the last three months not well controlled with long acting nitrates and propranolol Her blood pressure was 140/80 mm Hg with a regular heart rate of 75 per minute Physical examination was within normal limits except for a systolic ejection murmur Grade II/VI and a S gallop best heard at the apex The electrocardiogram revealed regular sinus rhythm and pathologic Q waves in *Leads I* aV_L *V to V consistent with* anterior wall infarction Chest x ray revealed minimal cardiomegaly The first cardiac catheterization and coronary angiography revealed normal cardiac output and normal pressures in the right heart with slight elevation of pulmonary wedge pressure (15 mm Hg) and left ventricular end-diastolic pressure (16 mm Hg) The left ventricular angiogram revealed akinesia of the apex of the left ventricle with a prolapsed mitral valve (Fig 1 *pre-op*) The coronary angiograms demonstrated over 50 to 75 per cent narrowing of the right coronary artery at the crux slight irregularities of the circumflex artery and 80 to 90 per cent proximal narrowing of the left anterior descending artery with good distal run-off On the day of cardiac catheterization she underwent saphenous vein bypass graft surgery to the right coronary and the left anterior descending arteries Her postoperative course was uneventful except for mental depression She was discharged two weeks after surgery on no medication and remained asymptomatic for three months On her second admission for recurrent angina pectoris a repeat left heart cardiac catheterization and left ventricular angiogram revealed again apical akinesia with a prolapsed mitral valve however there was a new large apical filling defect (Fig 1 *post op*) which was not present prior to surgery The saphenous vein bypass graft angiograms revealed a patent graft to the left anterior descending artery and closure of the graft to the right coronary artery A year after surgery she continues to have occasional exertional angina despite antianginal therapy

Case 2

A 44 year old white male with history of exertional precordial pain for one year sustained a transmural inferior infarction three months prior to admission In the last three months he continued to have precordial pressure radiating to the left arm occurring only on exertion and excitement relieved by sublingual nitroglycerin Because of these symptoms and his job as a truck driver he was advised to take a treadmill stress

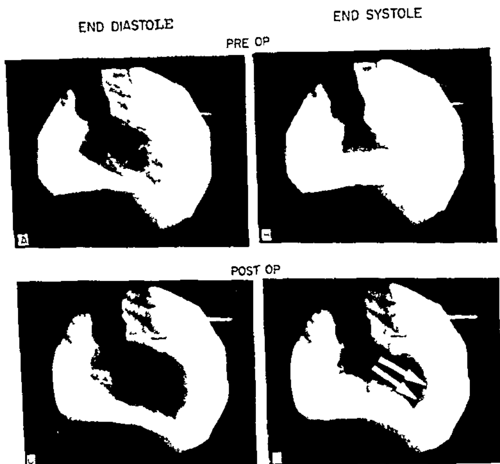


Fig 2 Pre and postoperative left ventricular angiograms of Case No 3 as viewed in the right anterior oblique projection Prior to surgery *(pre-op)* the left ventricular contraction is normal *(A and B)* Postoperatively *(post-op)* not only is there deterioration of left ventricular contraction but also new apical thrombus *(arrow in D)*

test during which he developed 3 mm ST segment depression and angina pectoris at a heart rate of 133/minute (70 per cent of predicted maximum) On admission he was comfortable with a blood pressure of 130/80 mm Hg and a regular pulse rate of 85 per minute He looked older than his age with extensive graying of his hair On physical examination the only positive finding was the presence of an S gallop His electrocardiogram showed an old inferior wall infarction Cardiac catheterization performed on December 3 1976 revealed normal cardiac output and normal pressures in both left and right heart. The left ventriculogram revealed an inferior wall aneurysm Selective coronary angiograms showed almost complete occlusion of the right coronary artery at its midportion with a good distal run-off The left anterior descending artery had a 70 to 80 per cent proximal stenosis with good run-off The circumflex artery was almost completely occluded proximally with good distal delayed filling Because of his symptoms and the findings on coronary angiography he underwent left anterior descending and right coronary bypass surgery Bypass graft to the marginal branch could not be performed His postoperative course was uneventful and ten days after surgery a postbypass graft angiogram showed patency of both grafts but the left ventriculogram revealed a new apical filling defect consistent with apical thrombus not present prior to surgery Four months after surgery he was asymptomatic on no therapy

Case 3

A 56-year old white male with a 3 week history of progressive resting and nocturnal angina not well controlled with antianginal drugs was admitted for coronary angiography and possible bypass surgery He was found to have hypertension 6 months earlier for which he received Dyazide Physical examination on admission was entirely within normal limits. His chest x ray and electrocardiogram did not reveal any abnormalities. Cardiac catheterization done on January 4, 1977 revealed normal cardiac output and normal pressures in the right and left heart except for slight elevation of left ventricular end-diastolic pressure (16 mm Hg) The left ventricular wall motion as well as valvular functions were all normal. Selective coronary angiograms demonstrated almost complete proximal occlusion of the right coronary artery with good run-off the left anterior descending and circumflex arteries also showed over 70 per cent proximal stenosis with fair run-off A similar lesion was noted on the diagonal branch of the left anterior descending artery Four days later he underwent saphenous vein bypass surgery to the above mentioned arteries On the fourth postoperative day he

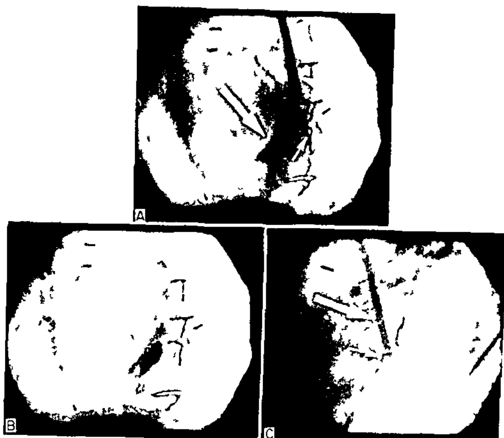


Fig 3 Selective saphenous vein opacification to the diagonal branch of the left anterior descending artery A In right anterior oblique projection upper large arrow points to patent graft and lower large arrow points to the leakage of angiographic material around distal anastomatic with good visualization of native vessel (small arrows) B The angiographic material continued to stagnate around the anastomatic site while the bypass graft and coronary artery already has been emptied C The graft (upper large arrow) the native vessel (small arrow) and the extravasated angiographic material (lower large arrow) are seen in left anterior oblique projection

complained of severe retrosternal pain and lightheadedness and his electrocardiogram revealed a new anterior wall infarction He was digitalized and treated as an acute myocardial infarction One month after surgery and just before discharge he had bypass angiograms which revealed deterioration of left ventricular contraction with impaired movement of the lower anterior and apical segment There was also a new apical filling defect consistent with thrombus (Fig 2) The saphenous vein grafts were patent to the left anterior descending right coronary and left circumflex arteries but the graft to the diagonal branch of the left anterior descending artery was closed

Case 4

A 65 year old white female was admitted for evaluation because of refractory exertional angina Her resting electro cardiogram was normal Cardiac catheterization performed on October 7 1976 revealed normal left ventricular contractile pattern normal cardiac output and normal pressures in the left and right heart Coronary angiograms revealed a severe degree of proximal stenosis of all three coronary arteries and also of the diagonal branch of the left anterior descending artery She underwent triple saphenous vein bypass grafts with five distal anastomoses the graft to the posterior descending artery and two marginal branches of circumflex artery was a snake (side-to side) graft Her postoperative course was uneventful and her electrocardiogram remained normal Angiogram two weeks after bypass revealed no change in the normal left ventricular contractile pattern and normal left ventricular end diastolic pressure The bypass grafts to the left anterior descending artery and its diagonal branch were patent but there was leakage with stagnation of angiographic material around the distral anastomatic site of the graft to the diagonal branch (Fig 3) The snake graft was closed

Case 5

A 52 year old white male with a history of angina for 6 years which required two admissions for coronary insufficiency in the last two years was admitted for coronary angiography because of progressive angina not well controlled with high doses of propranolol and nitrates He had a history of hypertension for twenty years treated with Aldomet On admission his electrocardiogram and physical examination was normal and his blood pressure was 150/90 mm Hg On cardiac catheterization cardiac output right and left heart pressures and left ventricular contractile pattern were all normal There was no evidence of any mitral regurgitation (Fig 4) His coronary angiogram showed 70 to 80 per cent narrowing of the main left left anterior descending and right coronary arteries The circumflex artery was irregular He underwent triple saphenous vein graft surgery Prior to discharge left heart catheterization and post bypass angio gram were performed which showed normal left ventricular end-diastolic pressure with normal motion of the left ventric ular walls but there was significant mitral regurgitation

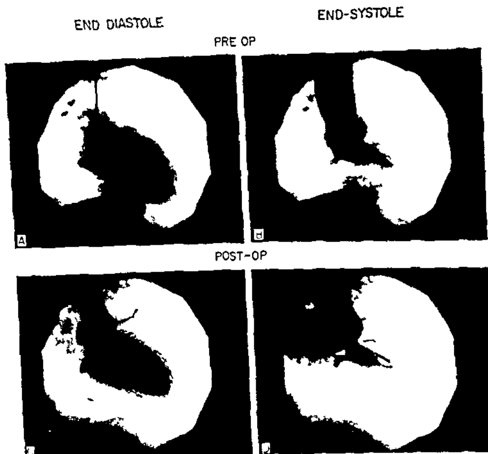


Fig 4 Comparison of pre and postoperative left ventricular angiograms of Case No 5 As shown in *D* there is significant angiographic evidence of mitral regurgitation *(arrow)* which was not present prior to surgery

Because of possible catheter induced mitral regurgitation the catheter was repositioned and repeat left ventriculogram again demonstrated moderate degree of mitral regurgitation Bypass angiogram showed patent grafts to all three arteries but there was significant stenosis of the right coronary artery at its anastomatic site (Fig 5) Auscultation at this time failed to reveal any heart murmur Six months after surgery he is completely asymptomatic and does not have murmur

Discussion

The most common complications of saphenous vein bypass surgery are related to the stenosis or occlusion of the vein grafts with subsequent myocardial infarction or deterioration of the left ventricular contraction, whereas unusual complications are seldom related to the occlusion of the graft but rather due to surgical technique Karpman[5] noted that a high percentage of patients with a patent bypass graft to the left anterior descending artery have a systolic murmur Bauman and Tsagaris described a continuous murmur in two patients which appeared after bypass surgery and they speculated that the murmur was produced by turbulent flow related to the graft In our previous report[4] as well as that of Vieweg and associates[6] the continuous murmur was due to a fistula between coronary artery and right ventricle or between the vein graft and coronary vein Although we noted small false aneurysms of the vein grafts at the distal anastomatic site with patent grafts in two patients on their two week postoperative angio grams none of them had late repeat graft angio grams to evaluate any deterioration in these structures However Baltaxe and Levin[9] described a case with false aneurysm of the vein graft whose initial patent graft was occluded during a second study eight months after surgery According to these authors the occlusion of the graft was caused by the compression of false aneurysm upon the bypass graft

Post bypass formation of the apical thrombi in Case 1 and 2 probably is related to the trauma



Fig 5 Selective specification of vein graft *(black arrow)* to the right coronary artery of Case 5 *The white arrow* points to the significant stenosis just distal to the anastomatic site probably this significant stenosis by causing papillary muscle dysfunction resulted in mitral regurgitation

caused by the vent introduced through the right pulmonary vein to the endothelieum of the apex of the heart with subsequent fibrin deposition and formation of the thrombus, whereas in Case 3 apical thrombus may have been due to postoperative anterior wall infarction None of these patients had left ventricular apical venting It is conceivable that patients with left ventricular apical venting who develop localized apical contractile abnormalities due to stab wound may develop apical thrombus However none of our 104 early saphenous vein bypass cases in whom apical venting technique was used, demonstrated apical thrombus It is well known that diffuse left ventricular dysfunction or multiple infarctions predispose to apical thrombus [13] Since none of the first two patients had diffuse left ventricular dysfunction or multiple infarctions it is improbable that apical akinesia in Case 1 and inferior wall aneurysm in Case 2 played any role in the genesis of apical thrombus Nevertheless these abnormal wall movements were present prior to surgery and did not predispose to the formation of thrombus In our Case 4 patient, as a result of improper and incomplete suturing of distal anastomosis, there was leakage of angiographic material probably on the epicardial surface surrounding the anastomatic site, without compromising the flow to the distal vessel Although this patient continued to be asymptomatic six months after surgery, we advised recatheterization a year after surgery to re evaluate the patency of the grafts

New post bypass significant angiographic mitral regurgitation in our fifth patient was most likely due to papillary muscle dysfunction Although the bypass graft to the right coronary artery was patent, there was significant stenosis just distal to the anastomatic site of the graft, possibly sufficient to compromise the blood supply of the papillary muscle Lack of systolic murmur in the presence of significant angiographic mitral regurgitation, as in our case, is uncommon In a few series not only was the intensity of the murmur poorly correlated to the degree of angiographic mitral regurgitation in patients with left ventricular dysfunction,[14] but silent mitral insufficiency of significant magnitude has been described in patients with coronary[15] and rheumatic heart disease [16]

Although our five patients had rare complications after bypass surgery and were asymptomatic, these complications should be considered in the entire spectrum of bypass surgical complications, because they are potential future sources of morbidity for these patients

Summary

Five patients after coronary bypass surgery developed unusual complications Three developed new apical thrombi which are thought to be due to the trauma of the left ventricular vent or deterioration of the left ventricular contraction Significant new mitral regurgitation in one patient probably is secondary to papillary muscle dysfunction as the result of stenosis distal to anastomoses The leakage of angoigraphic material around distal anastomatic site is due to technical error Although these unusual complications are very rare however they should be considered as potential source of morbidity in asymptomatic patients who leave the hospital after bypass surgery

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Intravascular hemolysis in the late course of aortic valve replacement. Relation to valve type, size, and function

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Implantation of prosthetic material into the heart induces intravascular hemolysis.[1] The discovery that the serum lactate dehydrogenase (LDH) levels reflected the rate of red cell breakdown[7] made quantitative evaluation of hemolysis in larger groups of patients possible. Thus, a first order correlation was found between LDH values and red cell half life in patients with prosthetic heart valves.[7] This makes the enzyme levels more useful for quantitation of intravascular hemolysis than most other parameters,[8] although it gives a rather rough estimation of red cell destruction.[7]

After aortic ball valve implantation a significant hemolysis frequently develop[9] and although it is usually well compensated, anemia represents a problem in some patients.[1, 9, 10] For unknown reasons, the degree of hemolysis varies considerably between patients with the same valve type.[9] The rate of red cell breakdown is, however, to some extent dependent upon the type and size of ball valve[9] and it may be aggravated by valvular or paravalvular leakage.[3] Hemolysis has been reported to be moderate after aortic disc valve implantation[11-13] but most comprehensive studies on intravascular hemolysis have been performed within the first year after valve implantation.

The present investigation was done to study the degree and significance of chronic intravascular hemolysis in the late course of aortic valve replacement, and to reveal the importance of factors that might influence red cell destruction. Hemolysis induced by two series of Starr-Edwards ball valves and the Lillehei-Kaster and Bjørk-Shiley disc valves was compared.

Materials and methods

Included were 315 patients with four types of prosthetic aortic valves and 64 healthy individuals.

Single Starr-Edwards aortic ball valves were implanted in 253 patients from 1967 to 1970. Two series were used, first type 1200 with silastic ball and metal cage, thereafter type 2300 with hollow Stellite ball and cloth covered cage.[14] Two types of aortic disc prostheses, the Bjørk-Shiley and Lillehei-Kaster valves, were implanted in 196 patients from 1971 to 1973 according to randomization.[15] Both valves have free floating discs and they differ mainly with regard to the shape of the cage. The Lillehei-Kaster valve is constructed to open slightly more, while the Bjørk-Shiley prosthesis has a larger orifice.[11, 16, 1] The disc of the Lillehei-Kaster valve closes against the metal of the ring, while the contact between disc and cage is more limited in the Bjørk-Shiley prosthesis.

The patients with ball valves were examined on average three and a half years after the operation and 169 of the 175 patients still alive reported for examination.[14] Similarly, 146 of the 152 patients alive with disc valves were studied, the mean time since the implantation being more than two years.[15]

The normal material of 64 healthy subjects, mostly hospital personnel, was selected to match the patient groups with regard to age and sex distribution.

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Received for publication May 26, 1977.
Accepted for publication Oct. 31, 1977.

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0002-8703/78/0196-0024$00 70/0 © 1978 The C. V. M

Table I Number of patients with each of the four valve types Mean age at operation and time since operation and occurrence of leaks arrhythmias and mitral valve disease

	Ball valves Starr Edwards type		*Disc valves*	
	1200	*2300*	*Lillehei Kaster*	*Bjørk Shiley*
No of patients	50	11[illegible]	72	74
Men	37	86	[illegible]6	49
Women	13	33	16	25
Time since operation months	5[illegible]6	37 2	25 [illegible]	25 7
Age at operation years	51 5	52 4	[illegible]3 3	54 6
No of patients with				
Leakag suspected	2	6	3	2
Leakage operated	0	3	3	2
Arrhythmias	11	[illegible]4	7	3
Mitral disease	12	29	14	16

The methods used were whole blood red cell and reticulocyte counts and creatinine levels were determined by routine methods LDH measurements were done in serum according to Wroblewski and LaDue[1] using commercial reagents (Kabi AB Sweden) The results are given in international units (I U) defined as the amount of enyzme that transforms one μmol of NADH per minute at 25° C The content of free haptoglobin was determined by Tarukoski s method[18] Plasma hemoglobin was measured in 66 unselected patients with Starr Edwards aortic ball valves For this test blood was carefully collected in plastic tubes and mixed with EDTA in a final concentration of 0 005 M Plasma was prepared by centrifugation at 300 × g for 10 minutes the plasma pipetted off and centrifuged in new tubes at 2000 × g for 30 minutes Plasma hemoglobin was determined by the method of Crosby and Furth This method gave reproducible results the coefficient of variation between duplicate samples being 5 0 per cent The plasma heme levels were expressed in terms of oxyhemoglobin standards determined with the cyanmet hemoglobin method[2]

Day to day variation of plasma LDH levels were studied by determination on two consecutive days in 17 healthy subjects and 15 patients with ball valves

Student s t test was used for statistical evaluation of the results

Table II Hemoglobin concentrations in healthy subjects and in patients with different types of aortic valve prostheses

	Hemoglobin (Gm./dl.)		*Compared with normal*
	Mean	*S D*	
Healthy subjects	14 9	1 1	
Patients with valve			
Starr Edwards type 1200	14 7	1 4	N S
Starr Edwards type 2300	13 8	1 8	$p < 0\ 005$
Lillehei Kaster	14 9	1 3	N.S
Bjørk Shiley	1[illegible] 1	1.2	N.S

Results

Blood samples from a total of 315 patients were analyzed (Table I) The mean time since operation differed between the four groups of patients being more than four and a half years in those with the oldest ball valve type A slightly higher mean age at operation in the last part of the period reflects the trend that valve replacement was gradually offered to older patients The sex distribution was similar between the two groups with ball valves while a higher proportion of men had Lillehei Kaster than Bjørk Shiley valves despite randomization

Eight subjects with ball valves and five with disc valves had diastolic murmurs suggesting valvular or paravalvular leakage or leaks had been demonstrated by angiography During the period three patients with ball valves and five with disc valves had been reoperated because of leakage Mitral disease not considered serious enough to require valve replacement was equally divided between subjects with the four valve types while continuous arrhythmia was more frequent in those with prosthetic ball valves

The mean whole blood hemoglobin concentration was significantly reduced in patients with the Starr Edwards valves of type 2300 although two thirds of them received iron substitution (Table II) Four had levels lower than 10 Gm /dl. their anemia representing a clinical problem One male patient who had received more than 60 transfu

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Received for publication May 26 1977
Accepted for publication Oct 31 1977

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The patients with ball valves were examined on average three and a half years after the operation and 169 of the 175 patients still alive reported for *examination*[1] Similarly 146 of the 152 patients alive with disc valves were studied the mean time since the implantation being more than two years[15]

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Table VI *Reticulocyte and erythrocyte counts* and mean corpuscular hemoglobin in healthy subjects and in patients with different aortic valve prostheses

	Reticulocytes (per cent)		*Erythrocytes (per µl)*		*MCH (pg)*
	Mean	*S D*	*Mean*	*S D*	
Healthy subjects	0 48	0 17	4 90	0 42	30 4
Patients with valve					
Starr Edwards 1200	*1 02*	*1 09*	*5 02*	*0 46*	29 3
Starr Edwards 2300	1 86	1 65	4 65	0 59	29 7
Lillehei Kaster	0 79	0 38	4 95	0 52	30 1
Bjørk Shiley	0 59	0 37	5 04	0 49	30 0

lysis was studied in three patients with disc valves LDH fell from 493 to 293 in one patient but remained at the preoperative level of 220 and 229 in two other In two other patients a thrombus on the valve that had left the discs in a semi open position was removed in both after a rapid development of congestive failure One had a preoperative LDH value of 1 380 U /L but simultaneously increased transaminases indicated LDH leakage from damaged liver cells After closure LDH was only 226 U /L In the other a level of 180 U /L was not influenced by the operation

The influence of the size of the valves on the degree of hemolysis was evaluated in patients without leaks (Table IV) The orifice diameters were smaller in the ball valves than in the disc prostheses and smallest in type 2300 because of the double cloth covering of the ring The Bjørk Shiley prosthesis is even more advantageous in this respect than is apparent from the table since the average annulus diameter was slightly smaller than in the Lillehei Kaster valves used The degree of hemolysis caused by smaller and larger valves within each of the four groups was compared (Table IV) The ball valves termed smaller were of size 10A or less corresponding to an inner diameter of 15.5 mm in type 1200 and 14 3 in type 2300 while the orifice diameter was 18 mm or less in both disc valve groups A significant difference in LDH levels was only found in patients with Starr Edwards valve type 2300 the smaller valves causing more hemolysis than the larger ones

Table VII *Plasma hemoglobin levels in 64 healthy* subjects and in 66 patients with Starr Edwards aortic ball valves

	Plasma hemoglobin (mg /dl)	
	Mean	*S D*
Healthy subjects	4 7	2 0
Patients with valve		
Starr Edwards 1200	5 8	3 0
Starr Edwards 2300	15 4	15 8

The day to day variation of LDH levels *expressed as the coefficient of variation* was 19 per cent in healthy subjects and 28 per cent in patients with aortic ball valves

Free haptoglobin was not found in plasma in the majority of patients with ball valves only four had levels slightly higher than 15 mg /dl (Table V) Unbound haptoglobin was absent or low also in most patients with disc valves especially in those with Lillehei Kaster prostheses

Normal mean red cell counts were maintained by an increased erythrocyte production in patients with Starr Edwards valve 1200 and with both disc valve types as reflected by increased numbers of circulating *reticulocytes (Table VI)* In those with type 2300 however the hemolysis was not fully compensated for even with a considerably increased red cell production The differences in red cell and reticulocyte counts between the groups with valve types 1200 and 2300 were highly significant ($p < 0.001$)

Plasma hemoglobin was determined only in *ball* valve patients since they had the most pronounced hemolysis (Table VII) The intravascular liberation of hemoglobin was not rapid enough to increase the plasma level in patients with valve 1200 while a slightly higher mean concentration appeared in those with the newer ball valves A good correlation was found between LDH and plasma hemoglobin levels in patients with valve type 2300 (Fig. 1)

Continuous intravascular hemolysis did not seriously affect renal function in the ball valve patients since the serum creatinine levels exceeded the upper normal limit of 1 3 mg /dl slightly in only six of them the highest recorded value being 1 9 mg /dl

Table III Serum LDH concentrations in healthy individuals and in patients with different types of aortic valve prostheses

	Serum LDH U /L		*Compared with normal*
	Mean	*S D*	
Healthy subjects	131 2	26 6	
Patients with valve			
Starr Edwards type 1200	343 7	227 3	p < 0 001
Starr Edwards type 2300	553 2	308 0	p < 0 001
Lillehei Kaster	230 0	54 7	p < 0 001
Bjørk Shiley	196 0	50 4	*p < 0 001*

Table IV Relation between serum LDH and size of the prosthetic aortic valves of different types Mean orifice diameter of each valve group

	Orifice diameter (mm)	*Serum LDH (U /L)*				
		Smaller valves		*Larger valves*		
		Mean	*S D*	*Mean*	*S D*	
Patients with valve						
Starr Edwards *1200*	16 4	314	134	332	217	N S
Starr Edwards *2300*	14 7	554	281	444	224	p < 0 05
Lillehei Kaster	18 2	232	48	228	55	N S
Bjørk Shilev	18 4	193	55	198	48	N S

sions during a three year period was finally reoperated because of the anemia but died post operatively Another man had also received several transfusions but only with temporary benefit A moderate anemia persisted in several patients with valve type 2300 in spite of iron administration The tendency towards anemia was less in individuals with valve series 1200 and did not constitute a problem in any patient In this group anemia was prevented by iron admin *istration* and the mean hemoglobin concentra tion did not deviate from normal The mean hemoglobin levels were also normal in both groups of patients with disc valves and none of them were anemic 25 per cent possibly because they received iron substitution

Table V Distribution of haptoglobin levels in the groups of patients with different types of aortic valve prostheses Normal range 30 180 mg /dl

Patients with valve	*Per cent distribution of haptoglobin*		
	< 15 mg /dl	*16 50 mg /dl*	*> 51 mg /dl*
Starr Edwards 1200	95	5	
Starr Edwards 2300	98	2	
Lillehei Kaster	70	17	13
Bjørk Shiley	43	33	24

The mean serum LDH levels (Table III) indi cated significant intravascular hemolysis in all four groups (p < 0 001) The ball valves caused considerably more hemolysis than did the disc valves, the difference between individuals with Starr Edwards valve type 1200 and the Lillehei Kaster valves being highly significant (p < 0 001) Considering the ball valves type 2300 caused more hemolysis than did type 1200 (p < 0 001) explaining the stronger tendency towards anemia In 36 of the patients with ball valves LDH values higher than 500 U /L indicated a red cell break down of more than twice the normal [7] In eight per cent of the patients including three of the four most anemic ones, LDH levels above 1 000 U /L reflected a fourfold increase of red cell destruc tion

A highly significant difference in LDH levels *between the two groups* with disc valves (p < 0 001) demonstrated that the Lillehei Kaster valves were more traumatic to red cells than the Bjørk Shiley prostheses The hemolysis was however, moderate in both groups and erythrocyte turnover of twice the normal rate was indicated in only one patient, while LDH values below the upper normal limit of 184 U /L wer found in 23 *per cent of the patients with* Lillehei Kaster and in 46 per cent of those with Bjørk Shiley valves

The relation between hemolysis and leaks was studied The mean LDH was 917 U /L in the eight ball valve patients with diagnosed or suspected leaks and in four higher levels than 1 000 U /L were found In the five patients with *disc valves who had diastolic murmurs the mean* LDH value was 217 U /L The effect of closure of paravalvular fistulae upon the degree of hemo

sent a problem in spite of well functioning valves and adequate iron substitution and may even require replacement of the valve This study demonstrate that severe anemia may develop in a few patients with hemodynamically satisfactory valves of type 2300 but hardly with any of the three other valves studied

Free haptoglobin is important to prevent iron loss by the urine Haptoglobin combines with hemoglobin in plasma [1, 33] the complex is brought to the reticulo endothelial system where iron is made available for reutilization [33, 3] When the hemoglobin binding capacity is exceeded free hemoglobin passes the glomerular membrane and iron is lost [3] The binding capacity of haptoglobin is limited [3, 3] and was exceeded even in a considerable proportion of the patients with disc valves *Iron deficiency* and anemia may therefore develop also in some patients with such valves unless iron is substituted

The increased red cell breakdown in patients with valve 2300 was not fully compensated for even with a considerably accelerated cell production while the mean corpuscular hemoglobin was normal most probably because of iron administration This demonstrates that the limiting factor in the prevention of anemia was the formation of new cells and not the incorporation of iron

Increased hemolysis known to accompany valvular or paravalvular leakage [3, 3] occurred *only in some of our patients with leaks* Nevertheless this complication should be suspected when the degree of hemolysis changes in a valve patient To what extent shear stress due to turbulence or direct mechanical trauma due to squeezing of blood through the aperture is responsible for the accelerated red cell breakdown is difficult to evaluate

Small amounts of hemoglobin accumulated in plasma in some patients with ball valves in spite of the rapid elimination of liberated pigment from blood depleted of free haptoglobin Red cells also contain considerable amounts of adenosine diphosphate (ADP) [1] which is a platelet aggregating substance and therefore *a potential* inducer of thrombosis Luckily however the degradation of free ADP proceeds so rapidly [3] that the nucleotide does not appear in concentrations known to affect platelet behaviour

The hemoglobin that *is filtered* through the glomerular membrane is reabsorbed by tubular endothelium [31, 4, 7] and converted to ferritin [6] and hemosiderin [4] Renal hemosiderosis as well as hemosiderinuria is characteristic in ahaptoglobinemic patients [35, 7] The present study demonstrated however that intravascular hemolysis did not seriously reduce the kidney function even several years after valve implantation

Summary

The degree of intravascular hemolysis was evaluated in 315 patients in the late course of aortic valve replacement Starr Edwards aortic ball valves of series 2300 caused significantly more hemolysis than did those of series 1200 as estimated from the serum lactate dehydrogenase levels Smaller valves of series 2300 caused a higher degree of hemolysis than did the larger ones. Aortic disc valves induced a more moderate red cell destruction than did the ball valves the Lillehei Kaster significantly more than the Bjørk Shiley prostheses Crushing of red cells is thought to be a more important cause of hemolysis than shearing forces in turbulent blood Hemolytic anemia represented a problem only in some patients with Starr Edwards valve type 2300 although iron substitution was necessary also in some with other prostheses since the hemoglobin binding capacity of haptoglobin was exceeded in several patients Valvular or paravalvular leakage was associated with stronger hemolysis in some patients and should be suspected whenever the rate of red cell destruction increases Longstanding intravascular hemolysis did not seriously affect renal function

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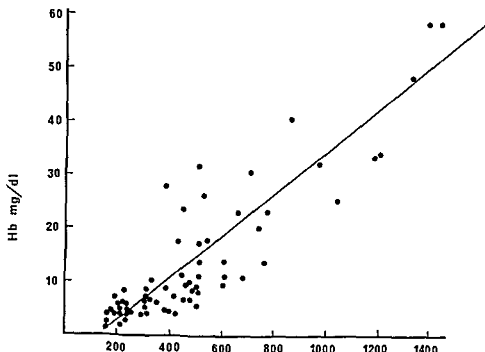


Fig 1 Relation between plasma hemoglobin concentrations and serum LDH levels in patients with Starr Edwards aortic ball valves of series 2300 Coefficient of correlation = 0 894

Discussion

The results confirm our earlier finding that intravascular hemolysis is more pronounced in patients with Starr Edwards valve type 2300 than with the older type 1200 [3] The mean LDH values in the two groups were quite similar to those measured within one year after operation,[3] indicating a rather constant degree of hemolysis in the late course of valve replacement The trend that the smaller valves of type 2300 caused more hemolysis than the larger ones has also persisted The difference in the degree of hemolysis between patients with the two ball valve types was however not entirely due to the difference in opening area alone Thus the hemolysis was significantly greater in the group with large 2300 valves than in that with small valves of series 1200 although the mean inner diameter was larger in the former group

The red cell membranes may be ruptured in two different ways either as a result of direct trauma by the impact of the ball or by shearing forces induced by turbulent blood flow [3] The stronger hemolysis caused by smaller than larger valves of type 2300 is probably related mainly to crushing Similarly a stronger direct trauma inflicted upon a higher number of red cells by the ball of this valve may be the cause of the more extensive hemolysis found in patients with valve 2300 than in those with type 1200 although larger peak systolic gradients across the former valve [4] indicate a higher rate of shear stress However, aortic stenosis with much higher gradients and considerable turbulence of the blood induces only a slight hemolysis even when combined with aortic insufficiency [5] It is therefore inconceivable that shearing forces should be a main determinant for red cell destruction after prosthetic valve implantation

Significantly more hemolysis in patients with Lillehei Kaster than in those with Bjørk Shiley valves has not been reported before although a more moderate difference has appeared in a previous study [11] Moderate intravascular hemolysis has been found to accompany implantation of both disc valve types [11 13] [3] Turbulence may occur by passage of blood through the smaller as well as the larger aperture of the disc valves Although the disc is able to open more in the Lillehei Kaster valve an angiographic investigation has demonstrated that it rarely moves maximally Turbulence is important for arterial thrombus formation [7] [8] and thrombi that disturb the movements of the disc represent a dangerous complication for the patient [15] The slightly brisker hemolysis caused by Lillehei Kaster than by Bjørk Shiley valves is, however most probably due to mechanical crushing because of the more extensive contact between disc and cage in the former type

Frank hemolytic anemia which occurs in some patients with aortic ball valves [3 9 10] may repre

Arterial thrombosis in essential thrombocythemia

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Much recent investigation into the pathogenesis of thromboembolic diseases and atherosclerosis has centered on the role of platelet adhesion and aggregation in initiating the thrombotic process A great deal has been learned about platelet function in normal and disease states[1] and under the influence of a variety of drugs[2] By contrast less attention has been paid to the effects of thrombocytosis on the vascular tree The purpose of this report is to describe our clinical and laboratory observations in ten patients with essential thrombocythemia followed for considerable periods of time

Subjects and methods

The ten patients with essential thrombocythemia had platelet counts consistently in excess of 875 thousand per cubic millimeter in the absence of any identifiable cause such as surgical or functional asplenia hemolysis chronic blood loss inflammation chronic infection and malignancy The platelet count at the time of diagnosis in nine of the patients exceeded 1 million per cubic millimeter The hemoglobin concentration was normal or low in all patients and none of the patients presented evidence for leukemia or myelofibrosis in the peripheral blood or in the bone marrow

Aggregation of platelets by adenosine diphosphate (ADP) and epinephrine was measured by the method of Born and Cross[3] using a model 300 1 Chronolog aggregometer attached to a Beckman 10 inch laboratory recorder At the time of the studies the patients had not ingested aspirin antihistaminics or anti inflammatory agents for one week or more The blood was collected into plastic tubes containing one tenth volume of 3 8 per cent sodium citrate The patient s platelet rich plasma prepared by centrifugation at $150 \times g$ and 22 C for five minutes was diluted with his own platelet poor plasma to a concentration of 200 to 300 thousand per cubic millimeter and was allowed to stand at room temperature for 30 minutes Then 0 05 ml of a solution of aggregating agent was added to 0 45 ml of the plasma in a small tube containing a Teflon coated magnet and the mixture was stirred continuously at 37° C The final concentrations of ADP were 5 and 20 μM and of epinephrine were 50 and 100 μM These were minimum concentrations which consistently produced 60 to 100 per cent aggregation of platelets in normal subjects The concentrations of epinephrine used were not sufficient to mask the platelet defect induced in normal subjects by the ingestion of aspirin

Platelet aggregation was quantified by assum

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Received for publication June 9 1977
Accepted for publication Oct. 31 1977

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Table I Clinical data in nine patients with essential thrombocythemia

Case	*Age (yrs)*	*Sex*	*Presenting symptoms*	*Hepato megaly*	*Spleno megaly*	*Con current factors*	*Total dose of busulfan (mg)*	*Time to 1st remis sion (days)*	*Duration of 1st remis sion (months)*	*Status*
1 A F	83	M	Bleeding from in guinal hernior rhaphy site 10 painful blue toes	0	0	–	104	27	40	Died in remission of a heart attack 41 months after diag nosis
2 E F	46	F	3 painful blue toes of 1 foot	+	+	Smoker	484	90	87	Alive in busulfan in duced 2nd remission 109 months after di agnosis
3 S G	68	F	1 painful blue toe	0	+	HBP† Diabetes	276	90	7	Alive in busulfan in duced 2nd remission 61 months after di agnosis
4 J S	71	M	Bleeding after dental extrac tion	0	0	HBP	144	36	26	Alive in relapse 44 months after diagno- sis Refuses further treatment
5 C S	67	M	1 painful blue toe	0	+	Smoker	260	90	32	Alive in busulfan in duced 2nd remission 43 months after di agnosis
6 R J	80	F	Coma CVA†	0	0	Smoker	–	–	–	Died without regain ing consciousness 3 weeks after diagnosis
7 M H	59	M	Nerve deafness	+	+	ASHD†	407	150	18	Alive in remission 23 months after diag nosis
8 E E	72	F	1 painful blue toe	0	+	HBP PAD†	136	50	2	Alive in busulfan in duced 2nd remission 23 months after di agnosis
9 M D	66	M	Dizziness	0	+	–	436	144	14	Alive in remission 19 months after diag nosis
10 S R	6	M	1 painful blue toe	+	+	–	–	–	–	Alive has not achieved remission 4 months after diag nosis Takes busul fan haphazardly

Spleen n t p lp bl Enlargement documented with the se of radioisot pe scan
†Abbre iat ns PAD = peripheral arteri l dise se w th laud cation HBP = byperte sion ASHD = art rioscleroti h rt disease CVA = cerebro ascular accident

were relieved as the platelet count reverted toward normal Nevertheless palpable pulsations did not reappear in occluded arteries of medium and larger size One patient (Case 10) took busulfan haphazardly Four months after diag nosis the platelet count and the spleen size were still increased and the great toe was painless but remained dusky in color

Busulfan was discontinued after the platelet count decreased to the normal range The dura tion of the remissions bore no apparent relation ship to the total dose of busulfan administered the initial height of the platelet count or the time required to achieve the initial normalization of the platelet count In five patients (Case 2 3 4 5 and 8) the platelet count increased to greater than 750 thousand/cubic millimeter after 2 to 87 months One of these patients (Case 4) refused

ing that the light transmission through the patient s platelet rich and platelet poor plasma sample represented 0 per cent and 100 per cent aggregation, respectively The maximum percent improvement in light transmission was considered equivalent to the maximum percent of aggregation achieved Maximum aggregation occurred 1 to 5 minutes after addition of ADP or epinephrine

Spontaneous aggregation of platelets was detected by continuous stirring of 0 50 ml of plasma at 37° C for a period of 15 minutes

Leukocyte alkaline phosphatase was determined by a histochemical technique[4] and serum levels of vitamin B12 and unbound vitamin B12 binding capacity by a radioimmunoassay method[5] ADP was purchased from Sigma Chemical Company, St Louis, Mo , and epinephrine from Park, Davis and Company, Detroit, Mich

Clinical presentation and laboraotry data

Ten patients with essential thrombocythemia (Table I) and 40 patients with polycythemia vera were diagnosed at this institution during a nine year period (1968 to 1977) The ages of the patients with essential thrombocythemia ranged between 46 and 83 years, the mean age was 69 years Sex distribution was nearly equal

The presenting complaint in six of the patients was painful blue toes which were cyanotic cold, and tender Posterior tibialis pulses in the affected lower extremities were absent in two of the six patients (Case 2 and 8) when they were first seen and three patients (Cases 1, 3, and 8) actually lost peripheral pulsations shortly after the diagnosis and while under our observation Bleeding occurred in only two patients and in each instance it was post surgical rather than spontaneous Evidence of modest splenomegaly palpable in five instances was obtained in seven patients and of hepatomegaly in three patients

Table II reveals laboratory data obtained at the time of diagnosis The platelet counts ranged between 0 88 and 2 26 million per cubic millimeter Large platelet clumps and giant forms were regularly observed in films made from finger stick blood Nine patients had modest yet unequivocal, leukocytosis due mainly to an absolute increase in band forms and segmented neutrophiles Only one patient was anemic (Case 4) and hypochromic erythrocytes were apparent in the peripheral smear The circulating erythrocytes in all the other patients were normochromic and displayed mild variation in size and shape, target cells and Howell Jolly bodies were not observed The aspirated bone marrow specimens were often hypercellular and they always demonstrated hyperplasia of megakaryocytes and the presence of large platelet clumps The relative proportion of myeloid and erythroid elements was normal in each case Iron was depleted in two patients M D , (Case 9) who was not anemic, and J S, (Case 4), whose hypochromic anemia corrected completely after the oral administration of iron The leukocyte alkaline phosphatase scores were variably increased normal or decreased The serum unbound vitamin B12 binding capacity was increased in only two of the six patients tested

Platelet function studies are summarized in Table III Epinephrine induced platelet aggregation was absent or markedly decreased (less than 40 per cent of maximum) in seven of eight patients studied when the platelet count was 750 thousand per cubic millimeter or greater and in all six patients studied at the time of diagnosis The aggregation of platelets by ADP was decreased less consistently than the aggregation by epinephrine Correction of the abnormal platelet responsiveness to epinephrine was achieved in some (Cases 5 7 8, and 10) but not all cases as the platelet count decreased toward the normal range (Fig 1) Spontaneous aggregation of platelets could not be detected in the four subjects who were studied (Cases 7 8 9 and 10) Platelet factor III was normally available in all patients and at all stages of the disease

Clinical course

One patient (Case 6) presented with coma and died after three weeks without regaining consciousness Her cerebrospinal fluid was neither bloody nor xanthrochromic The elevated platelet count was reduced to normal within 12 hours of diagnosis by plateletpheresis, and it was maintained at a low level thereafter by the administration of a single 0 4 mg per kilogram dose of nitrogen mustard intravenously and by daily busulfan by mouth Eight patients received oral busulfan alone at a starting dose of 2 to 4 mg per day Busulfan was uniformly effective in decreasing the platelet count to the normal range and in shrinking the size of the spleen The ischemic symptoms and the incipient gangrene of the toes

Table III Platelet functions

Case	Date	Platelets (×10⁶/cu mm)	Platelet aggregation		Platelet factor III availability
			ADP	Epinephrine	
1 A F	11/68	1 [illegible]	–	–	–
2 E F	4/68	1 01	–	–	–
	9/74	0 4	N	N	N
	11/75	0 8[illegible]	N	N	N
3 S G	4/7[illegible]	2 [illegible]	–	–	–
	11/75	0 30	N	A	N
	1/77	0 32	N	A	N
4 J S	9/ 3	1 33	[illegible]	A	N
	11/ 5	0 75	D	A	–
5 C S	10/73	1 01	–	–	N
	10 /4	0 3[illegible]	N	N	N
	9/76	0 80	D	D	N
	10/76	0 40	N	N	N
6 R J	6/74	1 18	N	D	N
7 M H	6/75	1 50	D	A	N
	10/75	0 30	N	N	N
8 E E	6/75	1 18	D	A	N
	3/76	0 4?	N	N	N
9 M D	11/7	1 03	A	A	N
	5/ 6	0 55	D	A	N
10 S R	1/77	0 88	N	D	N
	5/77	0 65	N	N	N

Aggregation of 60 pe ent or m re was consid red normal (N) and less than 60 pe c nt was decreased (D) Absence of d tectable aggregat on is d not d by (A)

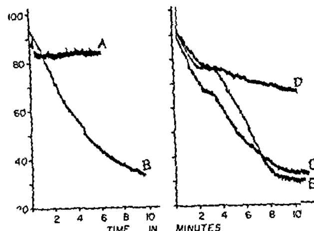


Fig 1 Platelet aggregation by epinephrine *Left panel* No aggregation of J S (Case 4) platelets at the time of diagnosis platelet count 1 33 million/cubic millimeter *(A)* normal aggregation in control subject *(B)* *Right panel* Aggregation of C S (case 5) platelets during remission in October 1974 *(C)* relapse in September 1976 *(D)* second remission in October 1976 *(E)* See Table III for platelet counts

Surprisingly three patients lost pulses in tibial and larger peripheral arteries shortly after thrombocythemia and digital infarction were found Occlusion of these larger arteries could reflect synergism between the thrombocythemia and concurrent risk factors i e diabetes mellitus hypertension and peripheral arteriosclerosis In deed the patient who developed popliteal artery occlusion had diabetes mellitus (Case 3) and another patient who lost pedal pulses had a history of intermittent claudication (Case 8) In the case of AF (Case 1) age 83 the loss of all dorsalis pedis and posterior tibial pulses may have occurred because of the superimposition of platelet thrombi on pre existing atherosclerotic plaques However E F (Case 2) was 46 and premenopausal when she was first seen and she had no significant risk factors for arteriosclerosis The finding that she lacked a palpable pulse in a posterior tibial artery at the time of diagnosis suggests that thrombocythemia per se may lead to the occlusion of medium size arteries

In contrast to the findings in secondary thrombocythemia qualitative disorders of platelet function frequently accompany the thrombocytosis of myeloproliferative disorders [7,18] The test that is abnormal most consistently at the time of diagnosis of essential thrombocythemia is epinephrine induced aggregation of platelets Our study confirms the nearly universal impairment of the platelet response to epinephrine reported by Spaet and associates[9] and Neemeh and colleagues The relationship between clinical thrombosis and the qualitatively abnormal platelets in this disorder is unknown Since thrombosis of digital arteries was observed at a broad range of platelet counts (0 88 to 2 26 million per cubic millimeter) factors other than the mere height of the platelet count may have played a role e g prior compromise of the circulation by disease in the blood vessel wall enhanced release of vasoactive amines by platelets and unusual stickiness of the platelets with a tendency to form large aggregates We are not aware of any published data on the release reaction of platelets in essential thrombocythemia or on platelet hyperaggregability in this disorder in response to aggregants In contrast to the findings reported by Preston and colleagues [12] none of the four patients whom we have studied showed spontaneous aggregation of platelets in vitro

Although statements in the literature indicate that a proportion of patients with essential thrombocythemia undergo a transition to polycy

Table II Laboratory data at the time of diagnosis

Case	*Hgb (Gm / 100 ml)*	*PCV (%)*	*MCHC (%)*	*WBC (×10 / cu mm)*	*Absolute neutrophils (×10 / cu mm)*	*Platelets (×10⁶/ cu mm)*	*LAP**	*Bone marrow aspirate*				*Serum†*		
								Cellularity	*Megakaryocytes*	*Iron*	*ME**	*B12 (pg / ml)*	*UBBC (pg / ml)*	*Uric acid (mg / 100 ml)*
1	12 6	36	35	12 8	10 2	1 72	N*	I*	I	2+	2 7	236	–	5 8
2	15 9	46	34	13 6	10 4	1 01	D*	I	I	3+	3 8	168	–	7 1
3	13 7	41	33	42 9	29 6	2 26	D	I	I	2+	4 1	625	2715	7 4
4	10 2	33	30	19 8	16 0	1 33	N	–‡	–	–	–	800	313	–
5	15 2	46	33	11 6	7 8	1 01	–	N	I	2+	1 7	400	–	4 1
6	13 4	38	35	17 3	14 1	1 18	I	I	I	3+	5 0	–	–	9 0
7	16 2	49	33	17 2	11 5	1 50	I	I	I	2+	4 1	327	2813	7 6
8	12 0	36	33	7 5	5 2	1 18	D	N	I	3+	2 8	125	927	7 4
9	14 9	44	33	11 7	9 0	1 03	I	I	I	0	2 5	180	1035	5 3
10	13 7	39	34	12 7	11 0	0 88	I	N	I	4+	2 5	640	619	10 6

Abbreviations LAP = leukocyte alkaline phosphatase ME = ratio of myeloid to erythroid cells I = increased N = normal D = decreased
†Normal serum B12 150 to 900 pg /ml unbound B12 binding capacity (UBBC) 850 to 1550 pg /ml uric acid 4 to 7 mg /100 ml
‡*Patient refused to permit aspiration of bone marrow*

further therapy Remission was induced in the remaining four patients by retreatment with busulfan which was then discontinued The duration of the second remissions has varied between 8 and 51 months and none of the patients has again relapsed

The nine patients who survived the initial presentation of their disease have been followed for a period ranging from 4 to 109 months Five patients have been followed for more than three years One patient (Case 1) died of a myocardial infarction at the age of 86 while in remission To date, none of the patients has shown evolution to another myeloproliferative disorder

Discussion

Essential thrombocythemia has generally been regarded as a disorder dominated by recurrent hemorrhages, most commonly epistaxis and gastrointestinal bleeding and by hypochromic iron deficiency anemia[6 11] Thrombosis of large veins has often been reported[6 8] Yet none of the ten patients in the present series conform to this description Our patients suffered much more from the sequelae of arterial occlusion than from hemorrhage, and none endured venous thromboses Indeed only two of ten patients experienced unusual bleeding (Case 1 and 4) In both hemorrhage appeared in areas of operative wounds and was self limited

We cannot satisfactorily explain the differences between the clinical manifestations of our patients and the patients reported in the other series[6 11] Although Preston[1] has hypothesized that patients with essential thrombocythemia and a relatively low platelet count are more likely to develop thrombosis whereas hemorrhage predominates in patients with relatively high platelet counts, a review of the data available in the published reports[6 11] does not substantiate this suggestion Nor is it likely that different diagnostic criteria have been applied to the patients in this series The relative incidence of essential thrombocythemia and polycythemia vera of 1 4 found in our population is similar to the ratio recently found by Lewis and colleagues[10] in a large series of patients with myeloproliferative disorders

The pre eminence of the digital infarction observed in the present series and in a few selected cases previously reported[6 8 11 13 14 15] probably relates to the great potential for vasoconstriction of peripheral arterioles and to clumping of a large number of platelets which ultimately occlude the already narrowed lumen Shortened survival of platelets has been reported in three essential thrombocythemia patients who had ischemic symptoms in the fingers and toes[15 16] whereas the survival of platelets in three patients without these symptoms was normal[15] The platelet survival data are consistent with a process of consumption of platelets in the course of the presumed thrombosis in the digital arteries

Table III Platelet functions

Case	Date	Platelets (×10⁶/cu mm)	Platelet aggregation		Platelet factor III availability
			ADP	Epinephrine	
1 A F	11/68	1 72	–	–	–
2 F F	4/68	1 01	–	–	–
	9/74	0 45	N	N	N
	11/75	0 85	N	N	N
3 S G	4/72	2 26	–	–	–
	11/75	0 30	N	A	N
	1/77	0 32	N	A	N
4 J S	9/ 3	1 33	N	A	N
	11/ 5	0 75	D	A	–
5 C S	10/ 3	1 01	–	–	N
	10/74	0 35	N	N	N
	9/ 6	0 80	D	D	N
	10/76	0 40	N	N	N
6 R J	6/74	1 18	N	D	N
7 M H	6/ 5	1 50	D	A	N
	10/75	0 30	N	N	N
8 E I	6/75	1 18	D	A	N
	3/76	0 42	N	N	N
9 M D	11/75	1 03	A	A	N
	5/76	0 55	D	A	N
10 S R	1/77	0 88	N	D	N
	5/77	0 65	N	N	N

Aggregation of 60 per cent or more was considered normal (N) and less than 60 per cent was decreased (D) Absence of detectable aggregation is denoted by (A)

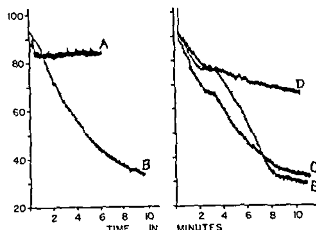


Fig 1 Platelet aggregation by epinephrine *Left panel* No aggregation of J S (case 4) platelets at the time of diagnosis platelet count 1.33 million/cubic millimeter *(A)* normal aggregation in control subject *(B)* *Right panel* Aggregation of C S (case 5) platelets during remission in October 1974 *(C)* relapse in September 19 6 *(D)* second remission in October 1976 *(E)* See Table III for platelet counts

Surprisingly three patients lost pulses in tibial and larger peripheral arteries shortly after thrombocythemia and digital infarction were found Occlusion of these larger arteries could reflect synergism between the thrombocythemia and concurrent risk factors i e diabetes mellitus hypertension and peripheral arteriosclerosis In deed the patient who developed popliteal artery occlusion had diabetes mellitus (Case 3) and another patient who lost pedal pulses had a history of intermittent claudication (Case 8) In the case of AF (Case 1) age 83 the loss of all dorsalis pedis and posterior tibial pulses may have occurred because of the superimposition of platelet thrombi on pre existing atherosclerotic plaques However E F (Case 2) was 46 and premenopausal when she was first seen and she had no significant risk factors for arteriosclerosis The finding that she lacked a palpable pulse in a posterior tibial artery at the time of diagnosis suggests that thrombocythemia per se may lead to the occlusion of medium size arteries

In contrast to the findings in secondary thrombocythemia qualitative disorders of platelet function frequently accompany the thrombocytosis of myeloproliferative disorders [17-19] The test that is abnormal most consistently at the time of diagnosis of essential thrombocythemia is epinephrine induced aggregation of platelets Our study confirms the nearly universal impairment of the platelet response to epinephrine reported by Spaet and associates and Neemeh and colleagues The relationship between clinical thrombosis and the qualitatively abnormal platelets in this disorder is unknown Since thrombosis of digital arteries was observed at a broad range of platelet counts (0 88 to 2 26 million per cubic millimeter) factors other than the mere height of the platelet count may have played a role e g prior compromise of the circulation by disease in the blood vessel wall enhanced release of vasoactive amines by platelets and unusual stickiness of the platelets with a tendency to form large aggregates We are not aware of any published data on the release reaction of platelets in essential thrombocythemia or on platelet hyperaggregability in this disorder in response to aggregants In contrast to the findings reported by Preston and colleagues [2] none of the four patients whom we have studied showed spontaneous aggregation of platelets in vitro

Although statements in the literature indicate that a proportion of patients with essential thrombocythemia undergo a transition to polycy

themia vera[10 11] or to myelofibrosis[10 11 0] we have not observed such a transition The course of essential thrombocythemia has been benign once the platelet count was reduced to the normal range, and relapses have responded well to retreatment with busulfan Because arterial thrombosis has been such a common presentation of essential thrombocythemia in our experience, and inasmuch as the response to myelosuppressive therapy has been so good, we believe that essential thrombocythemia should be suspected and platelet counts should be performed in every patient with occlusive arterial disease involving small size vessels Screening for essential thrombocythemia may also be important in patients with disease in larger vessels when the common risk factors which predispose to arterial thrombosis are not apparent e g, in the non diabetic patient with peripheral arterial disease and in the non diabetic normotensive patient with symptoms of cerebral ischemia

Summary

The course of essential thrombocythemia has been observed in ten patients ages 46 to 83, of whom nine were followed for a period of 4 months to 9 years In contrast to the experience with essential thrombocythemia recorded in the literature manifestations of arterial thrombosis were far more common than hemorrhage In six of the ten patients, the presenting complaints were ascribable to incipient gangrene of the toes and several of these patients additionally developed occlusion of tibial and larger arteries while under our observation All patients with incipient gangrene showed marked clinical improvement accompanying busulfan induced reduction and normalization of the platelet count Relapses in five patients after 2 to 87 months responded well to retreatment with busulfan No patient has shown evolution to another myeloproliferative disorder Essential thrombocythemia should be considered in the differential diagnosis of occlusive arterial disease

The authors wish to acknowledge the expert technical assistance of Ms Norma Tan B Sc

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Experimental and laboratory reports

Blind study on the relations between the extent of coronary arteriosclerosis and the strength of the myocardial contraction as measured by invasive and noninvasive tests

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George Karreman M D **
Thomas Bering B A ***
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During the past several years records of the carotid pulse derivative and the force ballistocardiogram have been secured in a series of over 76 cardiac patients admitted to the hospital for diagnostic cardiac catheterization and coronary angiograms the invasive and noninvasive tests having been performed within a few days of one another Great care was taken that the data to be compared were secured blindly i e Dr Shelburne s cardiac catheterization team remained ignorant of the findings of Dr Starr s ballistocardiographic team and vice versa until the data were assembled for statistical analysis many months later

As most of the information sought was physiological one would expect its magnitude to be influenced by abnormalities in the emotional state of the subjects at the time of the tests so we feared that the excitement inherent in invasive tests would put an interfering variable into the results which would make it difficult or impossible to demonstrate the physiological abnormalities of interest We planned to circumvent or minimize this difficulty by identifying those subjects who had reacted emotionally to the rigors of cardiac catheterization and eliminating their data After this elimination correlations of interest were sought by means of a computer in the data of the stable remainder who had undergone cardiac catheterization without emotional reaction detectable by our methods

A preliminary report[1] has been made A study of the significant relationship between the degree of *coronary sclerosis* and the presence of cardiac *incoordination* has already been published[2] Studies of the strong relation between *coronary sclerosis* and cardiac *strength* discovered in our data by the computer will now be presented

Subjects

Although inpatients at the University Hospital, all our subjects were ambulatory Age averaged 52 years ($\sigma \pm 12$ years) for the men 55 years ($\sigma \pm 12$ years) for the women

Divided according to the chief diagnosis 52 per cent were patients with typical coronary heart disease suffering from angina previous cardiac infarctions, or both with coronary narrowing demonstrated by angiogram 4 per cent were patients clinically suspected of coronary heart disease but without noteworthy coronary obstruction demonstrated by angiogram 23 per

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Recei ed f r p blic tion May 24 1977
Accepted f publi at n J l 18 1977

Reprint requests Isaa Starr M D Univ rsity of P nn ylvania School f Medicin & 1 Gates Memorial P vil on Uni rsity H sp tal Philad lphia Pa 19104

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Table 1 Two methods of dividing our data into two groups (a) those stable during catheterization, and (b) those excited by the procedure, by differences between the pulse rates and the systolic blood pressures at the invasive and noninvasive tests made on each subject

	(a) The stable group					*(b) The excited group*				
	No	*Mean pulse rate–difference per min*	*σ*	*Mean syst BP–difference mm Hg*	*σ*	*No*	*Mean pulse rate–difference*	*σ*	*Mean syst BP–difference*	*σ*
Method 1 (empirical) Limits of normal differences in pulse rate and systolic BP at the 2 tests were taken as 10 per minute and 10 mm Hg	29	1 0	±7	0 3	± 9	45	5 4	±16	7 3	±31
Method 2 (from a previous experiment) Limits of normal differences in pulse rate and systolic BP were 18 per minute and 32 mm Hg	51	1 3	±7 1	4 1	±16 2	24	13 6	±23 9	26 7	±37 8

cent had valvular heart disease in all probability rheumatic, without coronary narrowing, 15 per cent had valvular heart disease chiefly aortic, with coronary obstruction in addition, 6 per cent had miscellaneous diagnoses such as patent ductus IHSS, atrial septal defect, and constrictive pericarditis

Patients in unstable clinical states were not admitted to this study the data of the few such cases studied inadvertently have been omitted Thus no data secured from patients suffering from acute cardiac infarction acute temporary arrhythmia, congestive failure recent operative procedures, or febrile episodes were included in the final analysis In two cases the entrance of the catheter tip into the ventricles caused asystole and ventricular tachycardia respectively despite the fact that appropriate therapeutic measures resulted in the rapid return of normal rhythms the data obtained on these patients were not used

In a few cases some of the data sought routinely was not secured and this accounts for the small differences in numbers found in the tables

Methods

In the *invasive test* catheterization was performed by standard techniques[3] Blood pressure was taken from a catheter in the aorta or brachial artery Cardiac output was estimated by the dye dilution method the dye being injected into the pulmonary artery while samples were taken from the central aorta Ejection fractions were calculated from ventriculograms Dr Shelburne estimated the degree of coronary sclerosis from the angiograms by the method of Friesinger Page and Ross[4] in which the three main coronary branches are rated separately, zero indicating normal patency 1 to 4 various degrees of narrowing and 5 occlusion The sum of the three scores we have called the coronary rating a value of 15 indicating maximal arteriosclerosis and zero no sclerosis

The *noninvasive* tests were performed by Dr Starr's group after the subjects had been lying supine for ½ hour or longer in the comfortable hammock of the ULF ballistocardiograph[5] Force ballistocardiograms (Bcg)[5] records of the carotid pulse, and of its first time derivative (PD) were then secured[6], followed by estimations of blood pressure by the auscultatory method After calibration the average vertical I J amplitude (Bcg amp) was measured from each record, as was the average maximum slope of the front of the carotid pulse (PD max)[6]

Detection of those excited by invasive procedures The pulse rate and systolic blood pressure obtained on each subject during the noninvasive test were compared with those values found during the invasive test so that the differences could be compared with the normal scatter of those values found when two similar noninvasive tests are made on the same subject on different days To our surprise the latter were not to be found in the Biological Handbook[7] and we

Table II Clinical composition of the 76 patients studied and the number judged to be excited at catheterization by excessive differences in pulse rate and (or) systolic blood pressure at the invasive and noninvasive tests Normal limits used in this study were 18 per minute and 32 mm Hg so this is the less rigorous of our two methods of detecting excitement

	Number of subjects		
	Not excited by cath	Excited by cath	Total
A Coronary heart disease			
1 Typical cases of coronary heart disease with angina pectoris cardiac infarction or both	28	11	39
2 Cases with chest pain or abnormal ECGs, coronary heart disease suspected but not demonstrated by angiogram	2	1	3
3 Coronary heart disease complicated by valvular disease chiefly aortic	7	4	11
B No coronary heart disease			
1 Valvular heart disease chiefly RHD	11	7	18
2 Congenital heart disease patent ductus and atrial septal defect	2	0	2
3 Others IHSS	1	1	2
Constrictive pericarditis postop	0	1	1
Total	51	25 33%	76

Table III Items correlated with one another in this study

Measured at noninvasive test	Measured at catheterization
Age	Pulse pressure (brachial or aortic)
Body surface area	Mean systemic BP (brachial or aortic)
Pulse pressure	R ventricular systolic pressure
Mean blood pressure	R ventricular diastolic pressure
PD max (carotid artery)	R ventricular pulse pressure
Heart rate	R ventricular mean BP
Bcg amplitude	Wedge pressure
Bcg amp + BSA	Heart rate
Bcg amp + BSA × mean BP	Cardiac index
Pulse pressure × mean BP	Stroke volume index
Bcg amp + BSA × PD max	Ejection velocity index
Systolic BP	Stroke volume × mean BP
Diastolic BP	Ejection velocity × mean BP
	Coronary rating (amount of coronary sclerosis)

were forced to fall back on our own data and experience The fluctuations of pulse rate and blood pressure on different days are recorded on the chart of every hospital patient and from long experience with these we estimated that the normal scatter of heart rate and systolic BP observed on different days would be about 5 per minute for pulse rate and 5 mm Hg for systolic pressure So as a first trial we eliminated all our subjects whose pulse rate at catheterization differed from that at the noninvasive test by 10 per minute or more the blood pressure by 10 mm Hg or more or both This left a remainder of 29 patients who had taken cardiac catheterization in their stride their average differences in pulse rate and systolic BP in the invasive and noninvasive tests in the excited and nonexcited groups are given in Table I

The stable group thus selected consisted of 20 males and nine females whose average ages were 52 5 and 56 6 years and it was composed of 16 cases of typical coronary heart disease one case of probable coronary heart disease seven cases of typical rheumatic valvular disease one case of valvular heart disease with coronary obstruction also and four miscellaneous cases chiefly congenital heart disease Thus the diagnostic composition of these 29 stable subjects was essentially the same as that of the entire series tested in this study

Later seeking to compare this very stable group with a larger group selected by a less rigorous method of detecting those excited by catheterization we used the data assembled to control an experiment on digitalis action made a few years ago[a] in these subjects the normal limits (2σ) of differences between estimates of pulse rate and blood pressure made on the same subject on different days were 18 per minute and 32mm Hg

By eliminating those in whom differences of pulse rate and BP at the invasive and noninvasive tests exceeded these limits we obtained a sample of 51 stable subjects whose diagnoses are given in

Table I Two methods of dividing our data into two groups (a) those stable during catheterization and (b) those excited by the procedure by differences between the pulse rates and the systolic blood pressures at the *invasive and noninvasive tests made on each subject*

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	No	*Mean pulse rate-difference per min*	*σ*	*Mean syst BP-difference mm Hg*	*σ*	*No*	*Mean pulse rate-difference*	*σ*	*Mean syst BP-difference*	*σ*
Method 1 (*empirical*) Limits of normal differences in pulse rate and systolic BP at the 2 tests were taken as 10 per minute and 10 mm Hg	29	1.0	±7	0.3	±9	45	5.4	±16	7.3	±31
Method 2 (from a previous experiment) Limits of normal *differences in pulse rate* and systolic BP were 18 per minute and 32 mm Hg	51	1.3	±7.1	4.1	±16.2	24	13.6	±23.9	26.7	±37.8

cent had valvular heart disease, in all probability rheumatic, without coronary narrowing, 15 per cent had valvular heart disease, chiefly aortic with coronary obstruction in addition, 6 per cent had miscellaneous diagnoses such as patent ductus IHSS, atrial septal defect, and constrictive pericarditis

Patients in unstable clinical states were not admitted to this study, *the data of the few such* cases studied inadvertently have been omitted Thus no data secured from patients suffering from acute cardiac infarction acute temporary arrhythmia congestive failure recent operative procedures or febrile episodes were included in the final analysis In two cases the entrance of the catheter tip into the ventricles caused asystole and ventricular tachycardia, respectively despite the fact that appropriate therapeutic measures resulted in the rapid return of normal rhythms, the data obtained on these patients were not used

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The *noninvasive* tests were performed by Dr Starr s group after the subjects had been lying supine for ½ hour or longer in *the comfortable* hammock of the ULF ballistocardiograph[5] Force ballistocardiograms (Bcg),[5] records of the carotid pulse, and of its first time derivative (PD) were *then secured*[6], *followed* by estimations of blood pressure by the auscultatory method After calibration the average vertical I J amplitude (Bcg amp) was measured from each record as was the average maximum slope of the front of the carotid pulse (PD max)[6]

Detection of those excited by invasive procedures *The pulse rate and systolic blood* pressure obtained on each subject during the *noninvasive test* were compared with those values found during the invasive test so that the differences could be compared with the normal scatter of those values found when two similar noninvasive tests are made on the same subject on different days To our surprise *the latter were not* to be found in the Biological Handbook[7] and we

Table VI Correlations of the cardiac strength–coronary sclerosis relationship in various divisions of our data Subjects whose pulse rate differed by more than 18 per minute or whose systolic pressure differed by more than 32 mm Hg or both in the invasive and noninvasive tests are regarded as excited by catheterization

	n	*r*	Levels of significance *P* = 0 01	Levels of significance *P* = 0 05
I. In patients *not* excited by catheterization the stable group				
a. Those with coronary heart disease only	27	−0 5?	0 49	
b Add those with both coronary and valvular heart disease	34	−0 41	0 39	
II In patients *excited* by catheterization				
a. Those with coronary heart disease only	11	−0 48		0 60
b Add those with both coronary and valvular heart disease	15	−0 43		0 51
III Stable and excited patients combined				
a Those with coronary heart disease with and without complicating valvular heart disease	49	−0 38	0 34	
b Add those with valvular heart disease only (all our data except for miscellaneous cases)	67	−0 09		0 24

written consent to assume the risk The observations recorded in the invasive study were made soon after the minor operation required to insert the catheters had been performed under local anesthesia in an operating room atmosphere No sedatives were given routinely to our subjects but they were used occasionally if required Questioned after such invasive tests many patients had no complaints but others found the procedure so frightening and so disagreeable that they refused to undergo it again

In three of our cases the pulse rates during catheterization exceeded those of the noninvasive tests by 31 per cent 34 per cent and 63 per cent in three more the systolic BPs exceeded the controls by 31 per cent 41 per cent or 54 per cent in these the excitement was easy to identify But the logical placement of the line best fitted to divide our data into two groups excited and not excited presented difficulties Our aim was to work on groups of patients in whom the differences in pulse rate and blood pressure at invasive and noninvasive tests did not exceed those which are found when normal subjects are tested by duplicate non invasive tests made on different days Both groups of stable subjects described in Table I meet these criteria

Table VII Accuracy of estimates of the amount of coronary sclerosis in 29 patients stable during catheterization

Using
(a) Shelburne s Angiogram 1 (first reading)
(b) Shelburne s Angiogram 2 (second reading)
(c) Simple regression degree of coronatry obstruction =

$$9.24 - 0\,009 \left[\frac{\text{Bcg mm}}{\text{BSA (M)}} \times \text{mean BP mm Hg} \right]$$

(d) Multiple regression degree of coronary obstruction =

$$19\,2 + 0\,104\ \text{Age (year)} + 12.5\ \text{BSA} (M^2) - 0\,008 \left[\frac{\text{Bcg mm}}{\text{BSA (M)}} \times \text{mean BP mm Hg} \right]$$

Comparisons	Mean difference	σ
Angiogram 1 vs Angiogram 2	+0 1	2 7
Angiogram 1 vs value predicted by Simple Regression†	+0 2	3 9
Angiogram 1 vs value predicted by Multiple Regression†	+0 2	3 4

Whe 1 mm. = 2 75 (10') dyne
†Data from Angiogram 1 was used to compute both formulas

The cardiac strength/coronary sclerosis relationship The significant correlations of greatest interest identified by the computer in the data on our 29 most stable subjects have been placed in Table IV One of them stands out When the Bcg is calibrated in the standard way [15 mm = 275(10) dynes] the product of several measurements

$$\frac{\text{Bcg amp (mm)}}{\text{Body surface area } (M^2)} \times \frac{\text{Systolic blood pressure (mm Hg)} + \text{diastolic BP (mm Hg)}}{2} \quad (1)$$

correlates strongly (P = 0 02) with Shelburne s blind estimate of the degree of coronary artery sclerosis and this is the strongest of the hundreds of correlations calculated This relation seemed of such obvious clinical and physiological interest that the remainder of this paper has been devoted

Table IV Correlations between items measured at the noninvasive test and the amount of coronary sclerosis measured by angiogram in 29 very stable subjects who underwent cardiac catheterization without excitement

Measurement	*Number*	*Correlation coefficient*	*Probability of significance*
Bcg amp /BSA) × mean BP	27	−0 43	0 02
Age	29	0 37	0 04
Bcg amp /BSA	27	−0 37	0 05
Pulse pressure × mean BP	29	−0 36	0 05
Body surface area	27	0 37	0 06
Pulse pressure	29	−0 32	0 08
Mean blood pressure	29	−0 32	0 08
Systolic blood pressure	28	−0 33	0 09
Bcg amp	29	−0 26	0 17
PD max	28	−0 27	0 16

Table V Physiological measurements made during cardiac catheterization not correlating significantly with the degree of coronary sclerosis (i e , P > 0 10) in cases without emotional reaction to catheterization

	Number	*Correlation coefficient*	*Level of significance (P = 0 05)*
RV systolic pressure	29	−0 31	0 10
RV pulse pressure	28	−0 36	0 12
Ejection velocity index	27	0 25	0 20
Cardiac index	27	0 22	0 26
RV diastolic pressure	28	−0 22	0 27
Ejection fraction	20	−0 24	0 30
Ejection velocity index × mean BP	27	0 28	0 38
Stroke volume index × mean BP	27	0 16	0 56
Stroke volume index	27	0 18	0 63
Wedge pressure	29	0 17	0 63
LV end diastolic pressure	29	0 02	0 90

Table II In Table I the average values secured by our two methods of detecting the emotional reactors can be compared In both our stable samples the scatter of pulse rate and systolic BP differences in the two kinds of tests is less than that expected in duplicates, and the diagnostic composition of the two stable groups closely resembles that of the series as a whole We find no relation between excitement at catheterization and clinical differences

The statistical analysis was supervised by Dr Karreman and largely conducted by Mr Bering The first such study was made on the sample of 29 very stable subjects, secured by the more rigorous method of eliminating emotional reactors The data enumerated in Table III were placed on cards and fed to an IBM Unicol 360 system computer which was programmed to correlate each item with the 26 other items measured a total of 351 different correlations For those whose coefficients were larger than 0 3 regression equations were computed also

When the computer is used in this way the results contain much spurious correlation i e correlation between two variables which are not mathematically independent For example both cardiac index and stroke volume index are listed in Table III and the computer estimates that the correlation between them, r = 0 87 is strong But in this computation the same estimate of stroke volume is used twice, once by itself, again as a factor in the calculation of the cardiac index and so it is found on both sides of the regression equation For this reason the two variables are not mathematically independent and although their correlation cannot be explained by chance this fact is of little or no physiological interest Such spurious correlations have not been recorded in the tables

Hundreds of other correlations, not significant for P = 0 05, and of no apparent physiological interest have also been omitted from the tables Significant correlations of interest but not pertinent to this present study will be reported later

Results and discussion

Dangers in the comparison of results secured in invasive and noninvasive tests Both types of tests were done with the patients lying supine after a comparable rest period but here the resemblance ceased The noninvasive tests were performed on patients resting comfortably after reassurance that the test they were about to undergo was completely innocuous and that they could go to sleep if they wished as many of our subjects have done The invasive tests were performed after a warning required by the hospital s legal staff that the procedure was not without danger, and after each patient had given

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	n	r	Levels of significance P = 0 01	P = 0 05
I In patients *not* excited by catheterization the stable group				
a Those with coronary heart disease only	27	−0 52	0 49	
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RV diastolic pressure	28	−0 22	0 27
Ejection fraction	20	−0 24	0 30
Ejection velocity index × mean BP	27	0 28	0 38
Stroke volume index × mean BP	27	0 16	0 56
Stroke volume index	27	0 18	0 63
Wedge pressure	29	0 17	0 63
LV end diastolic pressure	29	0 02	0 90

Table II In Table I the average values secured by our two methods of detecting the emotional reactors can be compared In both our stable samples the scatter of pulse rate and systolic BP differences in the two kinds of tests is less than that expected in duplicates and the diagnostic composition of the two stable groups closely resembles that of the series as a whole We find no relation between excitement at catheterization and clinical differences

The statistical analysis was supervised by Dr Karreman and largely conducted by Mr Bering The first such study was made on the sample of 29 very stable subjects, secured by the more rigorous method of eliminating emotional reactors The data enumerated in Table III were placed on cards and fed to an IBM Unicol 360 system computer which was programmed to correlate each item with the 26 other items measured a total of 351 different correlations For those whose coefficients were larger than 0 3 regression equations were computed also

When the computer is used in this way the results contain much spurious correlation i e correlation between two variables which are not mathematically independent For example, both cardiac index and stroke volume index are listed in Table III and the computer estimates that the correlation between them r = 0 87, is strong But in this computation the same estimate of stroke volume is used twice, once by itself, again as a factor in the calculation of the cardiac index and so it is found on both sides of the regression equation For this reason the two variables are not mathematically independent and although their correlation cannot be explained by chance this fact is of little or no physiological interest Such spurious correlations have not been recorded in the tables

Hundreds of other correlations not significant for P = 0 05 and of no apparent physiological interest, have also been omitted from the tables Significant correlations of interest but not pertinent to this present study will be reported later

Results and discussion

Dangers in the comparison of results secured in invasive and noninvasive tests Both types of tests were done with the patients lying supine after a comparable rest period but here the resemblance ceased The noninvasive tests were performed on patients resting comfortably after reassurance that the test they were about to undergo was completely innocuous and that they could go to sleep if they wished as many of our subjects have done The invasive tests were performed after a warning required by the hospital s legal staff that the procedure was not without danger and after each patient had given

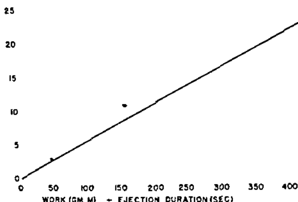


Fig 1 Does the formula used measure cardiac strength? Comparison between the formula s product used to measure cardiac strength in this study and accurate estimates of left ventricular power secured in a series of simulated systoles in experiments performed on cadaver RR Note the very strong correlation r = 0 9? A level of r = 0 51 is significant for P = 0 05 The line shown is the regression for estimating cardiac power from the formula Obviously the formula provides a good estimate of cardiac strength This was true in three other cadavers also

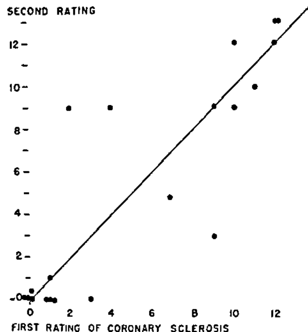


Fig 2 Comparison of two readings of 19 coronary angiograms made by Dr Shelburne about 6 months apart so that at the time of the second estimate he had forgotten the result of the first Note that when coronary sclerosis is absent or minimal and when it is very severe the two readings agree well but when sclerosis is moderate the two estimates are sometimes far apart

(Table IV) The product of pulse pressure and mean pressure attains significance and this is to be studied further One also recalls that the pulse pressure itself correlates significantly with cardiac work in cadaver experiments [1]

The correlations of the coronary rating with pulse pressure with mean pressure and with systolic pressure miss significance by very narrow margins (Table IV)

These simple relations between aspects of the pulse and the coronary rating are of great interest because of the ease with which the measurements needed to estimate the amount of coronary sclerosis from the regression could be made by any doctor But before testing our abilities to calculate the coronary rating from data secured by simple noninvasive methods two possible difficulties were investigated

Does the degree of excitement during the invasive test effect the cardiac strength/coronary sclerosis relationship? Table VI gives the results of a study of our data divided into stable and excited groups by our less rigorous method The relationship strong in the group of coronary cases not excited by catheterization remains equally strong when those excited by catheterization are added Apparently the obstructive abnormalities visualized by the angiogram are due to lesions of such a stable character that they are not influenced by excitement as might have been expected from the fact that so many coronary obstructions cannot be dilated by a probe at necropsy Despite our original misgivings in studies of the *cardiac strength/coronary sclerosis* relationship in catheterized patients we have the right to neglect excitement as a factor in the latter measurement

Does the type of heart disease affect the cardiac strength/coronary sclerosis relationship? The results recorded in Table VI answer this question in the affirmative In data from cases of coronary heart disease the relation is strong but if data from cases of valvular heart disease are added the correlation loses its significance What seems like a very interesting relation when coronary heart disease is studied by itself does not necessarily hold for other types of heart disease

On estimating the degree of coronary sclerosis from data secured by noninvasive methods By

to its study Contrasting with this finding is the list of items, measured during the invasive tests, which have been placed in Table V and in which the lack of correlation with coronary sclerosis is the feature of interest

Physiological meaning of the formula's product From knowledge of the general theory of the ballistocardiogram,[5] the formula (1) can be readily interpreted Bcg amp is the resultant of the initial forces of the cardiac contraction The inclusion of body surface area compensates for differences in body size in different subjects Mean blood pressure measures the load encountered by the ejecting heart

The relation of our formula (1) to more familiar aspects of cardiac performance can be expressed as follows whereas

$$\text{work} = \int P\,Q\,dt \quad (2)$$

where $Q = dv/dt$ = ejection flow in cm^3/sec, and P = arterial blood pressure

$$\text{power} = d(\text{work})/dt = d/dt \int P\,Q\,dt = P\,Q = \text{pressure} \times \text{flow} \quad (3)$$

$$\text{derivative of power} = d(\text{power})/dt = d/dt\,(P\,Q) = (dP/dt)Q + P(dQ/dt) \quad (4)$$

From our formula (1) we have

$$\text{Bcg} \times \bar{P} = (dQ/dt)\bar{P} \quad (5)$$

when, as in these experiments, the vertical I J distance of the Bcg is measured and the acceleration of the body's center of gravity is being recorded

One notes that the right side of (5) is essentially similar to the second term of the right side of (4) so the relationship of formula (1) to other aspects of cardiac performance is mathematically described

Certain implications of this relationship should be pointed out It is not unlikely that the first term in the right side of formula (4) is considerably smaller than the second term during early ejection This means that our formula (1) puts a heavy emphasis on the fast components of the heart's activity Its product is proportional to the time derivative of cardiac power

The mathematical demonstration that our formula (1) is theoretically related to the derivative of cardiac power does not deny that it may also be proportionally related to other more familiar aspects of cardiac function when systoles vary in strength This has recently been explored in data secured in cadaver experiments some years ago[9-11] In such models all the measurements needed to set up formula (1) can be made, so we were able to calculate its product for each of 43 simulated systoles in four cadavers In addition, the Newtonian work of the left ventricle in these simulated systoles could be estimated instant by instant and so with an accuracy not yet attained on living men or animals Cardiac power could be approximated by dividing work by ejection duration which was recorded very accurately But an accurate estimation of the derivative of power involved a second differentiation of the recorded volume curve which could not be performed with enough accuracy to make the effort worthwhile

Fig 1 shows the relation between the formula's product and left ventricular power in 14 simulated systoles in cadaver RR The correlation is strong r = 0 92, whereas r = 0 51 is significant for P = 0 05 The correlation between the formula's product and Newtonian work is also significant, r = 0 62, but the relation is not as strong as that with power When the 43 systoles simulated in these four cadavers are considered together, the correlation between the formula's product and left ventricular power is strong, r = 0 73 that with left ventricular work only a little less so, r = 0 65, a level of 0 40 being significant for P = 0 01

Evidently our formula is related to many aspects of cardiac strength and one should have no hesitation in using it for comparative measurements So the results in Table IV show clearly that, as coronary sclerosis increases, the strength of the resting cardiac contraction diminishes and we believe this to be the first experimental demonstration of this important relationship

Other significant relations with coronary sclerosis The other aspects of cardiac function identified by the computer as correlating significantly with the coronary rating (Table IV) lend support to this conception Although Bcg amplitude of itself does not correlate significantly with the amount of coronary sclerosis detected in this study when a factor to correct for differences of body size is added, significance is attained (Table IV) That age proves to be significantly correlated with the degree of coronary arteriosclerosis in our data will surprise nobody, the fact that this familiar relation is present testifies that our sample is a good one

Several aspects of the blood pressure either correlate significantly with the degree of coronary sclerosis or miss significance by a narrow margin

solely to the fact that the elaborate methods used to measure cardiac function in invasive testing are too inaccurate to permit the detection of abnormal relationships easily demonstrated by simple methods in the quiet of noninvasive testing

Despite such misgivings there is a physiological conception[1, 3, 11, 18] which provides a satisfactory explanation for this apparent contradiction in our findings Evidence from animal experiments[1, 6, 18] shows clearly that as the myocardium is weakened experimentally a reduction of the acceleration of ejected blood manifests itself first reduction of ejection velocity and displacement follow later So our findings are in accord with the view that in cases such as ours suffering from symptoms but still ambulatory resting cardiac function has deteriorated to the point where ejection acceleration is reduced but not to the point at which noteworthy reductions of cardiac output ejection velocity or both manifest themselves

This laboratory has long been interested in the higher dynamic cardiac functions and the information sought during noninvasive tests reflects our belief in the clinical importance *of such* measurements[2, 8] By means of the force Bcg and the pulse derivative one secures information about much higher frequency aspects of the heart s performance than is contained in the studies of cardiac output and ejection velocity made during the invasive tests The *measure*ments of high frequency performance recorded in Table IV identify important abnormalities *of* cardiac function at a stage of coronary heart disease when the lower frequency measurements in Table V do not Early weakness of your automobile can be readily detected by an inability to accelerate normally at a time when normal speed and distance traveled are *unaf*fected So our findings can be interpreted as additional evidence that the heart behaves in accordance with Newtonian principles and that the evidence of cardiac weakness will appear first as an inability to accelerate the blood *or in still* higher derivatives such as the jerk of the contraction at a time when cardiac output is still normal

Summary

Invasive tests based on cardiac catheterization and noninvasive tests based on the ballistocardiogram (Bcg) and pulse derivative (PD) were performed within a few days of each other on 76 cardiac patients To eliminate those who reacted emotionally to the invasive test only those whose pulse rates and systolic blood pressures were reasonably similar in the two tests were admitted to this study

Two methods of detecting excitement during catheterization were devised and tried the first more rigorous than the second The first method identified over one half of our subjects as excited during catheterization after these had been eliminated 29 stable subjects remained who had withstood the rigors *of catheterization without* excitement detectable by our methods In these 29 stable patients each of 13 items of physiological interest measured during the noninvasive test and each of 14 measured during *the invasive* test were correlated with all the others by means *of a computer* a total of 351 correlations

In these stable subjects four items measured at the noninvasive test correlated significantly with the amount of coronary sclerosis rated by angiogram

$$\frac{\text{Bcg amplitude}}{\text{Body surface area}} \times \text{mean blood pressure} \quad \text{age}$$

$$\frac{\text{Bcg amplitude}}{\text{Body surface area}}$$

and pulse pressure × mean pressure In four other items significance was missed by a narrow margin

Correlations between the coronary rating and physiological measurements made at the *invasive* test such as stroke volume cardiac output ejection fraction ejection velocity *and LV end* diastolic pressure were very poor and did not approach significance

In cases of coronary heart disease the *cardiac strength/coronary sclerosis* relationship is *strong in* both the stable group and in those excited during catheterization *But* the same relation does not hold in cases of valvular heart disease

Mathematically the product Bcg amp/BSA × mean blood pressure is proportionally related *to* the first time derivative of cardiac power *Using data* secured several years ago[10] when systoles differing in strength were simulated in cadaver *experiments* the formula s product was also found to be strongly *correlated* with both cardiac work and power So our data indi

means of regression equations derived from any of the significant correlations, such as equation *C* in Table VII, one could calculate the degree of coronary sclerosis for any patient from measurements made at noninvasive tests, and more accurate information could be secured by incorporating the most promising items into a multiple regression equation, such as equation *D* (Table VII)

Before comparing estimates made by such equations with the coronary rating estimated from the coronary angiograms, one should know the reproducibility of the latter measurement In our studies duplicate angiograms were not attempted, but Shelburne restudied the films taken at 19 of our angiograms after a lapse of time sufficient to abolish his recollection of his original readings

Comparisons of his first and second estimates are found in Fig 2 When the amount of sclerosis was large, or when it was absent or minimal, Shelburne's two readings were very consistent, but in the middle range he sometimes missed badly But the average difference between his first and second reading was only 0 1 coronary unit ($\sigma = 2\ 7$), and this we found encouraging The scatter of such ratings in tests in which everything is duplicated will certainly be larger than this

In Table VII estimates of the coronary rating made by simple and multiple regression equations can be compared with Shelburne's estimates from the angiogram and a large part of the differences can be accounted for by the errors inherent in the latter estimates Thus when a simple regression equation, *C* in Table VII is used to compute the coronary rating of our most stable patients with coronary heart disease the difference between such estimates and Shelburne s first readings of the angiograms averages only +1 4 coronary units But when the same equation is used for the cases of rheumatic valvular heart disease the average error of the estimate is −4 2 units and this difference cannot be explained by chance Such difficulties greatly handicap the use of such equations to diagnose coronary sclerosis

The reason for the difficulty seems plain When estimating the coronary rating by such regression equations one is attempting to measure the severity of the lesions of coronary artery disease from the abnormalities of cardiac performance which accompany them But while the severity of coronary heart disease is strongly correlated with cardiac weakness in cases suffering from coronary heart disease, and this seems well worth knowing, this is not true of our cases of RHD, many of whom have hearts as weak as those with advanced coronary heart disease but although coronary sclerosis was found by angiogram So, clinicians should remember that, if the heart beats strongly, the presence of advanced coronary heart disease is most unlikely But they must also remember that coronary arteriosclerosis is only one of many causes of cardiac weakness, and that an attempt to diagnose its presence and extent from cardiac weakness alone would often result in serious errors

Why are measurements of cardiac function made by invasive testing so often completely unrelated to the degree of coronary arteriosclerosis? The contrast between Tables IV and V is one of the most interesting and unexpected of the findings of this blind study Judged by the physiological data secured during cardiac catheterization, coronary sclerosis has no effect on cardiac function (Table V) Judged by the data secured by noninvasive testing (Table IV) coronary sclerosis is accompanied by cardiac weakness manifest in many ways

One possible explanation of the discrepancy lies in the belief that the simple measurements of pressures and forces made during noninvasive tests are more accurate and are made under more reproducible conditions than the much more complicated measurements of circulatory function attempted during invasive tests In the noninvasive tests the long procession of pulses and Bcg s taken at each test provides evidence of the stability of the cardiac performance at the time of the test The absolute accuracy of the noninvasive methods has been studied in mechanical mathematical electrical and cadaver models[5, 1, 13, 14], while not of high accuracy these methods are surely accurate enough to identify the extremes of abnormality

No comparable information is available about either the accuracy or the consistency of estimations of cardiac output, ejection velocity ejection fraction etc made in the invasive studies largely because the rigors of such tests discourage work on the healthy and the repeated testing of the sick

So one cannot deny that the difference in the results recorded in Tables IV and V might be due

Comparison of heart rate and blood pressure response to amyl nitrite isoproterenol and standing before and during acute beta-adrenergic blockade with intravenous propranolol

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Propranolol a beta adrenergic blocking drug has been used extensively in the treatment of angina pectoris cardiac arrhythmias, and hypertension[1,2] Numerous other beta blockers are now under investigation and most of them will probably be available to the practicing physician in the near future Since beta blockers affect sympathetic nervous activity it is important for the clinician to be able to test in every day practice whether sufficient drug has been given or if the administrated beta blocker has been eliminated after its discontinuation The appropriate test therefore should be simple non invasive and easy to reproduce To date the heart rate response to various physiological maneuvers (standing up passive head up tilt hyperventilation Valsava) and to pharmacologic agents (nitroglycerin isoprenaline) before and during acute or chronic propranolol administration has been used for this purpose Fitzgerald has suggested that heart rate increase following sublingual administration of nitroglycerin before and after propranolol may be used as a test of adrenergic beta blockade but the specificity of this test has recently been questioned by other investigators[4]

It was suggested that amyl nitrite rather than nitroglycerin may be a more appropriate drug to study heart rate response before and during beta adrenergic blockade since a greater heart rate peak may be achieved over a shorter period of time in comparison with nitroglycerin In the present study the heart rate response during amyl nitrite inhalation was compared to that observed with standing up and isoproterenol infusion before and during acute adrenergic beta blockade with intravenous propranolol

The results indicate that neither amyl nitrite inhalation nor the assumption of upright posture during intravenous propranolol can be used to assess the degree of beta adrenergic blockade because heart rate responses to both procedures are determined to a great extent by the parasympathetic nervous system

Patients and methods

Six patients with mild essential hypertension and three normal volunteers were investigated Six were male and three female their ages ranging from 21 to 59 years, mean 39 5 years Informed consent was obtained from all subjects None of the patients was receiving oral propranolol or other beta blockers at the time of the study or during the two weeks prior to it

All subjects were allowed to rest in the supine position until heart rate and blood pressure were stabilized usually within 20 minutes Heart rate was recorded continuously (Lead II of the ECG) and blood pressure was measured by a mercury sphygmomanometer After control values were obtained the subject was asked to stand up while the ECG was recorded The highest heart rate

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Received for publication June 13 1977
Accepted for publication Dec. 9 1977

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0002-8 03/ 8 0196-0047$00 0/0 © 1978 The C V Mosby Co

cate that, as coronary obstruction increases, the strength of the resting cardiac contraction diminishes

Our data have important diagnostic implications, if the heart of any patient is beating *strongly*, the presence of severe coronary heart disease can be ruled out But if the heart is beating *weakly*, the presence of significant coronary heart disease cannot be safely inferred, for coronary heart disease is only one of many causes of cardiac weakness

We are indebted to Dr A Noordergraaf for advice and assistance in the theoretical aspects of this study

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Table II Heart rate increase (Δ %) with the various stimuli before and after i v propranolol (10 mg)

	Standing up		Amyl nitrite		Isoproterenol 0 03 μg/Kg /min	
	Before	After	Before	After	Before	After
Heart rate (beats/min mean ± SD)	21 66 ± 7 39	12 44 ± 7 40	57 2_ ± 24 00	36 11 ± 18 40	25 44 ± 9 74	2 22 ± 5 66
p value	ns		p < 001		p < 001	

hypertensive patient Heart rate increase with standing correlated with the increase produced by amylnitrite (r = 0 723 p < 05) but no correlation was observed in the heart rate increase produced by standing and isoproterenol (r ~ 0 163) or amyl nitrite and isoproterenol (r ≈ 0 229) The relative potency for heart rate and blood pressure responses of the three stimuli is shown in Table III

2 Blood pressure response to amyl nitrite before and during beta blockade with propranolol (Table IV) Before propranolol the control average mean arterial pressure in the nine subjects was 107 ± 19 falling to 74 ± 9 mm Hg (p < 001) following amyl nitrite inhalation Isoproterenol infusion (0 03 μg/Kg /min) and intravenous propranolol produced a small fall in blood pressure (Table IV) After propranolol amyl nitrite inhalation was followed again by a significant decrease in blood pressure (p < 005) while isoproterenol infusion produced again insignificant changes in blood pressure with the exception of Case 6 who exhibited a greater decrease (by 30/20 mm Hg) in blood pressure

3 Correlation between blood pressure and heart rate responses Before propranolol the increase in heart rate after amyl nitrite inhalation correlated with the observed fall in blood pressure (r = 0 607) but the correlation did not reach statistical significance probably because of the small number of subjects studied After propranolol the r value was 0 417

In Fig 2 the average per cent change in systolic blood pressure is plotted against the average per cent change in heart rate before and after amyl nitrite before and during acute beta blockade with propranolol This graph shows that the baroreceptor reflex remained functioning when amyl nitrite was given after pretreatment with intravenous propranolol In Fig 3 the difference in heart rate and blood pressure responses between the normal subjects (n = 3) and the hypertensive patients (n = 6) is shown It is clear that the hypertensive patients had a smaller heart rate increase following amyl nitrite prior to and during beta blockade despite a greater decrease in blood pressure However because of the small numbers of subjects involved no statistical analysis was attempted

4 Side effects Amyl nitrite inhalation was associated with the following side effects coughing dizziness feeling faint and headache No side effects were observed during isoproterenol infusion

Discussion

Amyl nitrite administration as test of adrenergic beta blockade As suggested previously[5] amyl nitrite inhalation proved to be the most potent stimulus for heart rate increase in comparison to standing up and isoproterenol infusion (Table IV) However a great variation in individual heart rate responses was observed both before (from 27 to 97 per cent) and during beta blockade (from 10 to 60 per cent) These changes probably reflected the different degree of blood pressure decrease and varying sympathetic and vagal participation in the individual patient It is known that other factors such as age and the presence of hypertension[1, 2] probably sex[13] uremia and autonomic neuropathy[1] or cardiac disease[5] may affect the degree of cardioacceleration produced by hypotension All these factors may exist in the heterogeneous population of patients who require treatment with beta blockers (coronary heart disease cardiac arrhythmias hypertension) and they per se may determine heart rate responses to amyl nitrite as well as the degree of beta blockade Furthermore the unpleasant and occasionally serious side effects of amyl nitrite together with the inherent effects of the method of its administration (cough hyperventilation) which separately may influence cardiovascular responses[14] will make amyl nitrite

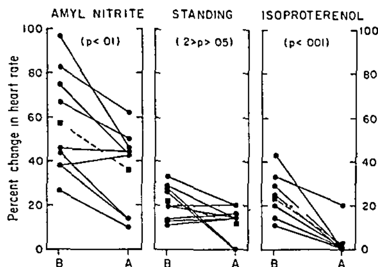


Fig 1 Heart rate responses to three different procedures before and after intravenous propranolol The greatest variability in heart rate response was observed with amyl nitrite *B* = before propranolol *A* = after propranolol = each line represents two patients ● -● mean change

observed within a two minute period of standing was noted and the subject returned to the supine position again Following another control period amyl nitrite was given to the subject to inhale (three deep breaths) and the maximal rise in heart rate and fall in blood pressure were recorded Amyl nitrite was given in the supine position in order to avoid the nitrite syncope When the effects of amyl nitrite had passed, and both heart rate and blood pressure had returned to control levels, with the subject in the supine position, isoproterenol was given by infusion at three dose levels, 0 01, 0 02 and 0 03 μg/Kg of body weight/minute, as previously described[9] heart rate and blood pressure were recorded with each dose level of the infusion When again heart rate and blood pressure had returned to control levels (usually within 10 minutes after stopping the infusion) propranolol 10 mg was given slowly intravenously with the patient in the supine position All the above procedures (standing up amyl nitrite inhalation and isoproterenol infusion) were repeated 10 to 15 minutes after propranolol when the maximal bradycardic effect was observed

Standard statistical methods were used to calculate averages standard deviations and correlation coefficients and the statistical significance of the results [10] During the analysis of the results heart rate and blood pressure changes produced by the 0 01 and 0 02 μg/Kg /min isoproterenol dose and pressure changes with standing up were small and therefore they will not be discussed further

Table I Heart rate response to stimuli before propranolol

	Heart rate (beats/min ± SD)		p value	% increase in HR	
	Control	Response		Mean ± SD	Range
Standing up	77±15	94±18	p< 05	21 66±7 39	11-33
Amyl nitrite inhalation	76±12	118±19	p< 001	57 22±24 0	27-97
Isoproterenol 0 03 μg/Kg /min	74±11	94±13	p< 005	25 44±9 74	11-43

Results

1 Heart rate response to standing up amyl nitrite inhalation and isoproterenol infusion before and after propranolol

A Before the administration of propranolol *heart rate was significantly increased* by all three procedures (Table I) The greatest heart rate increase (57 per cent) occurred following amyl nitrite inhalation (p < 001), isoproterenol 0 03 μg/Kg /min produced a 25 per cent increase (p < 005), while the least potent stimulus for heart rate increase was standing up (21 6 per cent p < 05) Great individual variability in heart rate increase was observed with all procedures (Table I Fig 1) *especially following amyl nitrite* inhalation (range 27 to 97 per cent increase) There was no correlation between the heart response to standing with that produced by amyl nitrite (r = 0 441, p > 05) or between standing and isoproterenol infusion (r = 0 371 p > 05) but a significant negative correlation was observed between amyl nitrite and isoproterenol increase in heart rate (r = −0 832 p < 01)

B After propranolol administration (Table II and Fig 1) the increase in heart rate produced by the above procedures was diminished Heart rate increase with amyl nitrite was significantly decreased but not completely abolished by propranolol from 57 per cent to 36 per cent (by 42 beats/minute p < 01) heart rate increase with standing up was decreased by propranolol from 21 to 12 per cent (by 8 beats/minute) but not significantly The response of heart rate to isoproterenol infusion (0 03 μg/Kg /min) was completely blocked by propranolol in eight subjects but isoproterenol given after propranolol still produced a 20 per cent increase in heart rate in one

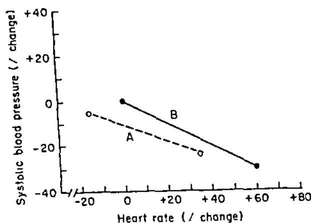


Fig 2 Normal baroreceptor reflex function before *(B)* and after *(A)* adrenergic beta blockade with propranolol following amyl nitrite administration Propranolol did not affect the slope of the line relating the per cent change of heart rate to per cent change in systolic blood pressure

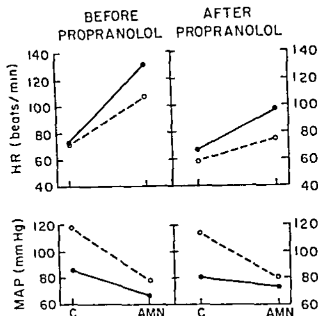


Fig 3 Differences in heart rate and blood pressure response to amyl nitrite between normal (●——●) and hypertensive (o – o) subjects. Heart rate increase was greater in the normals despite a smaller decrease in blood pressure

This finding suggests that parasympathetic withdrawal is also a major mechanism for heart rate increase with standing at least during acute beta adrenergic blockade In two similar studies oral practolol[6] and oral propranolol[7] decreased significantly but did not abolish completely heart rate increase after standing

The heart rate increase produced by isoproterenol infusion was completely abolished by propranolol in eight subjects but a 20 per cent increase in heart rate was observed in one patient even after propranolol Isoproterenol increases heart rate by direct cardiac stimulation and by reflex vagal withdrawal as a result of the decrease in blood pressure because of peripheral vasodilation[31] In the present study vagal withdrawal probably contributed to the heart rate increase in the single patient who was not blocked by propranolol since he exhibited a marked fall in blood pressure (by 30/20 mm Hg) while blood pressure changes were negligible (a 5 mm Hg average mean blood pressure fall) in the remaining subjects.

Difference in heart rate response between normal and hypertensive subjects Another interesting observation of the present study was the greater heart rate increase following amyl nitrite administration which occurred in the normal subjects as compared with the hypertensive patients although the latter exhibited a greater hypotensive response following amyl nitrite administration (Fig 3) This finding would suggest that decreased parasympathetic inhibition existed in the hypertensive patients of the present study as has been reported previously in borderline[3] [3] and established[15] hypertension Since however the number of normal subjects who took part in the present study is rather small further investigations are needed to substantiate the observed differences in heart rate response between normal and hypertensive subjects during amyl nitrite induced hypotension

Conclusions

The findings of the present study confirm that the increase in heart rate produced by the three procedures investigated is diminished but not completely abolished during acute beta blockade with intravenous propranolol because of varying degrees of vagal participation in heart rate control A varying degree of participation in heart rate control by the individual components of the autonomic nervous system may explain the different degrees of correlation in heart rate changes among the three procedures (Table V) Thus the negative correlation in heart rate increase between amyl nitrite and isoproterenol (*before* propranolol) would mean that the greater the increase in heart rate via the parasympathetic the lesser via the sympathetic as is shown in

Table III Relative potency of the three stimuli for heart rate and blood pressure response

	Heart rate		
	Sympathetic	*Para sympathetic*	*Blood pressure*
Before propranolol			
Amyl nitrite	+ +	+ +	+ + +
Isoproterenol	+ + +	+	+ +
Standing	+ +	+ +	+
During propranolol			
Amyl nitrite	−	+ + + +	+ + +
Isoproterenol	−	(+)	+
Standing	−	+ + + +	+

Symbols + = effective − = absent (+) = occasionally effective

Table IV Blood pressure changes (averages ± SD, mm Hg) with the various procedures

	Control	*After*	*p value**	*% change*
Before propranolol				
Amyl nitrite	*107 38 ± 19*	*73 97 ± 9*	p < *001*	−30
Isoproterenol 0 3 μg/Kg / mm	114 ± 27	103 ± 21	ns	−11
Propranolol	113 ± 24	*106 ± 25*	p < *025*	−5 6
After propranolol				
Amyl nitrite	106 22 ± 25	81 ± 18	< 005	−26 6
Isoproterenol	102 ± 18	97 ± 14	ns	−9 3

*paired t test
ns = not significant

the least appropriate test for estimating the degree of beta blockade in routine clinical practice Similar conclusions were reached by other investigators[8] regarding the usefulness of nitro glycerin administration

Amyl nitrite, however, may *still be used to* study baroreceptor function,[17] since it is a potent and quick acting hypotensive agent *Because of* its other hemodynamic effects the drug has been used for the evaluation of cardiac murmurs [18]

From the clinical standpoint, the results of the present study do not favor the usage of amyl nitrite as a test for the detection of the degree of beta blockade, but nevertheless they do confirm that the amyl nitrite induced acute hypotension in the presence of beta blockade is transient and without deleterious hemodynamic consequenses as has been documented by other investigators[19] and by ourselves (unpublished observations) with the more commonly used peripheral vasodilators [20]

Mechanism of the tachycardia following baroreceptor hypotension The relative participation of the two components of the autonomic nervous system in the heart rate increase that results from baroreceptor hypotension is now better understood [21 24] It has been shown[23 24] that the cardioacceleration during acute baroreceptor hypotension is due to an increased sympathetic stimulation, and also a withdrawal of the parasympathetic tone The reduction in blood pressure after amyl *nitrite administration is mainly* due to the vasodilatory effect of the drug on the arteriolar smooth muscle [5] It has been suggested that the tachycardia which accompanies the fall *in blood pressure after amyl nitrite* is mainly due to reflex withdrawal of the parasympathetic tone at least in normal subjects [26] because the drug had negligible effect on the heart rate when given after atropinization The finding of the present study, *however, that* propranolol blocked *the* effect of amyl nitrite on the heart rate significantly *would support the view that the* heart rate response is mediated to a significant degree by sympathethic activation A direct effect of amyl nitrite on the heart (sinus node) is very unlikely [7] Nitroglycerin induced tachycardia is *similarly* the result not only of sympathetic stimulation alone,[5] but also of parasympathetic withdrawal [6 8] Therefore heart rate response to both agents cannot be used as a specific test for beta adrenergic blockade

Atropine was not used in the present study because our aim was to explore heart rate responses in the absence of *atropinization as they occur in clinical practice It was initially reported*[5] that atropine did not modify the increase in heart rate produced by nitroglycerin but this finding does not exclude *the possibility that atropine* administration may effect heart rate response following hypotension in the presence of beta blockade when the sympathetic-parasympathetic balance *on heart* rate may be *altered* [28 30] Indeed it has been shown[28] that the combination *of atropine and propranolol can almost completely* abolish the heart rate increase produced by amyl nitrite

Mechanism of tachycardia with standing and during isoproterenol infusion In the present study heart rate increase with standing was decreased by propranolol but not significantly

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Table V Correlation coefficients between heart rate increase (beats/minute) with the three procedures before and after propranolol

	r value	*p value*
Before propranolol		
Standing amyl nitrite	−0 441	ns
Standing isoproterenol	0 371	ns
Amyl nitrite isoproterenol	−0 832	p < 01
After propranolol		
Standing amyl nitrite	*0 723*	p < 05
Standing isoproterenol	0 163	ns
Amyl nitrite isoproterenol	0 229	ns

Table III This finding is in agreement with the classical view that heart rate responses are the result of sympathetic–parasympathetic balance[38] The positive correlation in heart rate increase between *standing and amyl nitrite (after propra nolol)* may be explained by the fact that in the absence of the sympathetic nervous system the magnitude of heart rate increase is mediated via the parasympathetic by both procedures (Table IV) It is obvious therefore that neither amyl nitrite inhalation nor standing can be used for the assessment of beta blockade, since heart rate responses to both procedures are determined to a great extent by the parasympathetic nervous system

Summary

Heart rate responses to three different proce dures (amyl nitrite inhalation, standing up and isoproterenol infusion) were studied before and during acute adrenergic beta blockade with intra venous propranolol in three normal and six hypertensive subjects Propranolol decreased but did not completely abolish the heart rate increase produced *by amyl nitrite and standing* probably because of vagal participation (with drawal) in heart rate increase produced by baro receptor hypotension (amyl nitrite) and on assuming the upright posture

Heart rate responses to amyl nitrite varied greatly from patient to patient (from 27 to 97 per cent), but the drug proved to be the most potent stimulus for heart rate increase as a result of its marked hypo*tensive effect* However this vasodi lator induced acute hypotension was well toler ated and without deleterious hemodynamic consequences despite the presence of beta block ade

Different degrees of correlation in heart rate increase were observed with the three procedures, reflecting probably the varying sympathetic-parasympathetic participation in reflex heart rate control It is concluded that from the clinical *stand point, neither amyl nitrite administration* nor standing up can be used as a test to assess *acurately the degree of beta blockade,* because both procedures activate vagal withdrawal which increases heart rate regardless of the degree of beta blockade

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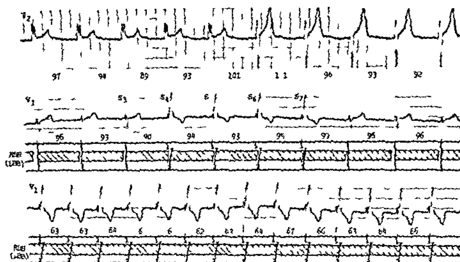


Fig 1 Case 1 Rate dependent right bundle branch block Three strips are not continuous Shaded areas in the diagrams represent the refractory period of the right bundle branch for the anterogradely conducted impulse Impulse conduction within the right bundle branch is indicated by solid lines whereas impulse conduction within the left bundle branch is indicated by dashed lines Time intervals are expressed in hundredths of a second S = sinus impulse or beat RBB = right bundle branch LBB = left bundle branch

second examination (i e a period of 64) This indicates that the critical CL inducing RDBBB varied within a month though it was invariable throughout one examination

Case 3 In this case findings similar to those in Case 2 were seen The electrocardiograms showed rate dependent right BBB which were taken from a 20 year old man with an otherwise normal heart The critical CL inducing RDBBB during the first examination (a period of 91) was considerably longer than that during the next examination (a period of 84) These examinations were made at an interval of a week This indicates that the critical CL inducing RDBBB varied within a week During either examination however the critical CL allowing recovery was longer than the critical CL inducing RDBBB by a period of 5

Case 4 In Case 4 the critical CL inducing RDBBB varied even in a continuous recording The electrocardiogram showed rate dependent right BBB which was recorded from a 64 year old man with an otherwise normal heart As shown in Fig 3 the critical CL inducing RDBBB fluctuated between periods of 125 and 135 in a continuous 17 minute recording The critical CL allowing recovery also fluctuated in parallel with the critical CL inducing RDBBB Therefore when reversion to normal conduction occurred within a very short time after RDBBB was induced the critical CL allowing recovery was always longer than the critical CL inducing

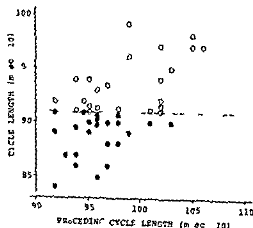


Fig 2 Case 1 The critical cycle length inducing bundle branch block, and the preceding cycle length in a 10-minute recording When normal conduction is maintained the shortest cycle length is indicated by open circles When bundle branch block is induced the cycle length between the last normal conduction and the initial bundle branch block is indicated by solid circles The critical cycle length inducing bundle branch block which is indicated by the dashed line is independent of changes in the preceding cycle length

RDBBB and the difference between them was constant (a period of 5) However the shortest critical CL allowing recovery in the continuous recording (i.e a period of 130) was considerably shorter than the longest critical CL inducing RDBBB (i.e., a period of 135) This case indicates that the critical CL inducing RDBBB varied within only a few minutes

Variations in the critical cycle length inducing rate dependent bundle branch block

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It has been demonstrated that in many patients with tachycardic RDBBB (rate dependent bundle branch block), the critical CL (cycle length) allowing reversion to normal conduction is considerably longer than the critical CI inducing RDBBB[1,2] On the other hand it has been reported that in RDBBB, the refractory period of the blocked bundle branch varies under certain conditions[1,3,4] In order to disclose the mechanism of maintenance of RDBBB it seems important to know whether the comparatively long critical CL during recovery is due to variation in the bundle branch refractory period or due to another mechanism In the present report five patients with tachycardic RDBBB will be presented in whom variations in the critical cycle lengths inducing RDBBB and allowing recovery are investigated

Case Reports

Case 1 *Fig 1 represents portions of long recordings showing rate dependent BBB (bundle branch block) which were taken from a 33 year old man with an otherwise normal heart The three strips in Fig 1 are not continuous In Case 1 the critical CL inducing RDBBB was an invariable value i e a period of 91 * which was independent of changes in the preceding CL The critical CL allowing reversion to normal conduction was another invariable value, i e a period of 98* which was considerably longer than the critical CL inducing RDBBB In Case 1, extending over two years, the critical CL inducing RDBBB and the critical CL allowing recovery were both invariable

Fig 2 shows the relationship between the critical CL inducing RDBBB and the preceding CL in a 10 minute recording including the upper two strips in Fig 1 The dashed line in Fig 2 indicates that, independent of changes in the preceding CL, the critical CL inducing RDBBB is invariable, in which the preceding cycle lengths range between periods of 91 and 103 The middle strip in Fig 1 shows that although the cycle lengths between two sinus beats of the BBB type, i e the intervals S_4 S_5, S_5 S_6, and S S are all within the same range as the above, the critical CL allowing reversion to normal conduction is distinctly longer than the critical CL inducing RDBBB

Case 2 The electrocardiograms which were recorded from a 69 year old man with essential hypertension showed rate dependent *left BBB* Electrocardiographic examination was *made* three times at *intervals of about a month* *During* any of the three examinations the critical *CL* allowing recovery was longer than the critical CL inducing RDBBB in the same recording and the difference between them was a period *of* 5 However, the critical cycle lengths inducing RDBBB during the three examinations were different from one another which were periods of 71 84 and 73 Therefore *the critical cycle lengths allowing recovery* during the first and third examinations (i e periods of 76 and 78) were shorter than the critical CL inducing RDBBB during the

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Supported *in* part by a grant from the Education Ministry of the Japanese Government

Received *for* publication June 14 1977

Accepted for publication Jan 13 19 8

Reprint requests Shinji Kinoshita M D the Second Department of Medicine Hokkaido *University School* of *Medicine Sapporo Japan*

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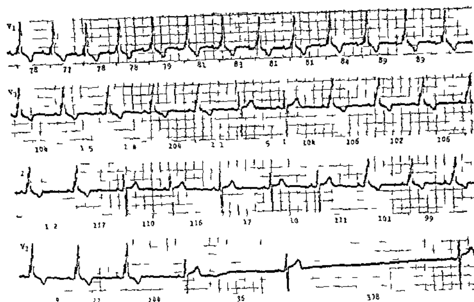


Fig 4 Case 5 Rate dependent right bundle branch block showing variations in the critical cycle length inducing bundle branch block The four strips are not continuous In the bottom strip the sinus rhythm is slowed owing to pressure on the eyeball. Time intervals are expressed in hundredths of a second

that unidirectional block in the bundle branch is the main mechanism of maintenance of RDBBB for the following reasons

The possibility exists that the beat of seemingly complete BBB configuration might be caused not by true complete BBB but by markedly slow antegrade conduction into the bundle branch If the beat of seemingly complete BBB configuration is caused by slow antegrade conduction the transition from normal configuration to complete BBB configuration will usually be gradual namely increasing grades of incomplete BBB patterns will usually be seen However in only a few cases of RDBBB such gradual transition can be seen In most cases of RDBBB including the present cases the transition is sudden without showing incomplete BBB patterns which makes unlikely the presence of slow antegrade conduction into the bundle branch Even in the cases showing gradual transition due to slow antegrade conduction if unidirectional block in the bundle branch is not present bundle branch Wenckebach periods will usually be seen and therefore BBB will usually not be maintained[3]

Transient depression of atrioventricular (A V) conduction through the His Purkinje system following rapid driving has been defined as the fatigue phenomenon When such depression causes A V block block of the 2 1 type occurs before complete recovery of conduction However in most cases of RDBBB after shortening of only one CL RDBBB can be maintained for a long time and thereafter reversion to normal conduction occurs without showing 2 1 BBB Therefore it seems unlikely that "fatigue of the blocked bundle branch is the main mechanism of maintenance of RDBBB namely in most cases of RDBBB the refractory period of the blocked bundle branch appears to vary within a comparatively narrow range even when BBB is maintained The presence of a fatigue of the blocked bundle branch was suggested in a few cases of RDBBB However it appears to me that in these cases too RDBBB was maintained not because of fatigue but because of unidirectional block in the bundle branch If unidirectional block were not present in these cases RDBBB could not be maintained and 2 1 BBB would occur

Thus the critical CL inducing RDBBB appears to show the refractory period of the blocked bundle branch for the anterogradely conducted impulse Therefore the observations in the present report suggest that independent of variations in the bundle branch refractory period the critical CL allowing reversion to normal conduction is considerably longer than this refractory period This suggests the presence of concealed retrograde conduction to the blocked bundle branch as illustrated in the diagram below the middle

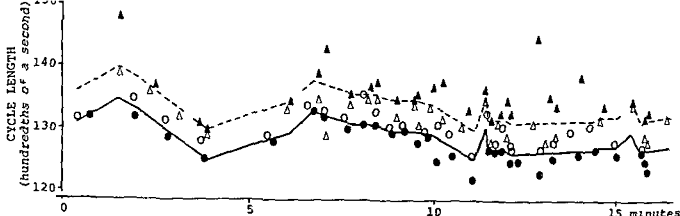


Fig 3 Case 4 *Fluctuations of critical cycle lengths inducing bundle branch block and allowing reversion to normal conduction* When bundle branch block is induced the cycle length preceding the initial bundle branch block is indicated *by solid circles* Conversely when reversion to normal conduction occurs the cycle length preceding the initial normal conduction is indicated *by solid triangles* During the period from the solid triangle to the next solid circle normal conduction is maintained During this period the shortest cycle length preceding normal conduction is indicated *by open circles* Accordingly the critical cycle length inducing bundle branch block during this period will be found between the open circle and the solid circle or at the solid circle variations in this critical length are indicated *by the solid line* On the other hand during the period from the solid circle to the next solid triangle bundle branch block is maintained During this period the longest cycle length preceding bundle branch block is indicated *by open triangles* Therefore the critical cycle length allowing recovery during this period will be found between the open triangle and the solid triangle or at the solid triangle variations in this critical cycle length are indicated *by the dashed line* The critical cycle length inducing bundle branch block fluctuates in parallel with the critical cycle length allowing recovery

Case 5 In this case the critical CL inducing RDBBB varied from cycle to cycle Fig 4 represents portions of long recordings showing rate dependent right BBB which were taken from a 36 year old man with paroxysmal supraventricular tachycardia The four strips in Fig 4 are not continuous Cycle lengths at rest ranged between periods of 77 and 130 When the CL at rest was shorter than a period of 100 the following sinus beat was always of right BBB configuration as shown in the top strip of Fig 4 When on the other hand the CL was prolonged beyond a period of 127 the following sinus beat was always of normal configuration as shown in the bottom strip of Fig 4 The longest CL during pressure on the eyeball (Aschner s test) was a period of 772 These findings indicate that Case 5 was also one of tachycardic RDBBB However the critical CL inducing RDBBB fluctuated between periods of 100 and 127 As a result when the CL varied between periods of 100 and 127 the following sinus beat was sometimes of the right BBB type and at other times of normal configuration as shown in the second and third strips of Fig 4 In the second strip reversion to normal conduction occurs despite the fact that the CL at recovery (a period of 101) is shorter than the CI preceding that (a period of 104) Besides in the third strip RDBBB is induced despite the fact that the CL at induction (a period of 111) is longer than the CL preceding that (a period of 110) These facts indicate that the critical CL inducing RDBBB varied within a very short time, occasionally even from cycle to cycle Therefore, even within a very short time a fixed difference between the critical CL inducing RDBBB and the critical CL allowing recovery could not be disclosed

Discussion

The present report demonstrates that critical CL inducing RDBBB was invariable in Case 1 extending over two years and that in the other cases it varied within a comparatively short period However when RDBBB was maintained for only a few cycles the critical CL allowing reversion to normal conduction was always longer than the critical CL inducing RDBBB here in all cases except Case 5 In Case 5 such a distinct difference in CL could not be disclosed because the critical CL inducing RDBBB varied from cycle to cycle

It is known that when RDBBB is initiated it is almost always maintained for some time There are several possible mechanisms by which RDBBB could be maintained—(1) slow antegrade conduction (2) fatigue of the bundle branch (3) unidirectional block and (4) combination of (1) and (3) or of (2) and (3) However I believe

In other words "true" unidirectional block is considered to be present at the site of RDBBB. Similarly in all other cases except Case 5 RDBBB was maintained even when the CL was shortened below the bundle branch refractory period for the anterogradely conducted impulse.

If repeated retrograde conduction as mentioned above maintains RDBBB, it is expected that when the CL is shortened below the refractory period for the retrogradely conducted impulse, retrograde conduction to the blocked bundle branch will not occur in succession. Fig. 5 represents portions of a recording after exercise in Case 5. The middle and bottom strips are continuous but the top and middle strips are not continuous. In Fig. 5 the sinus beat of a normal configuration often appears despite the fact that the CL here is far shorter than the critical CL inducing RDBBB at rest. This can probably be explained by shortening of the CL below the refractory period for the retrograde impulse which will result in 2:1 retrograde conduction to the RBB as illustrated in the diagrams below the strips. When an anterograde sinus impulse falls after the RBB refractory period because of both anterograde and retrograde block of the preceding sinus impulse, it will become a beat of normal configuration—for example the sinus beats S and S in the top strip. When, on the other hand, the anterograde impulse falls in the RBB refractory period despite both anterograde and retrograde block of the preceding impulse, it will become a beat of the right BBB type—for example the beats S and S in the top strip. In the middle strip the sinus impulse following such bidirectional block becomes sometimes the beat of a normal configuration and at other times the beat of the right BBB type although the CL is almost invariable in this strip. This can be explained by the fact that the RBB refractory period for the anterograde impulse considerably varies from cycle to cycle in this case as mentioned above. In the bottom strip of Fig. 5 the CL increases beyond a period of 60 (i.e., one half of 120). After that all the sinus beats are of the right BBB type until the CL reaches a period of 111. Here retrograde conduction to the RBB seems to occur in succession as illustrated in the diagram below the strip, probably because the CL becomes longer than the refractory period for the retrograde impulse though it remains shorter than that for the anterograde impulse. Such features after exercise reinforce the conclusion that "true" unidirectional block is present at the site of RDBBB. Thereafter features similar to those shown in Fig. 4 were also seen in this recording, namely, when the CL increased beyond the period of 111 the sinus beat was sometimes of normal configuration and at other times of the right BBB type because of considerable fluctuation in the RBB refractory period for the anterograde impulse, and when the CL was prolonged beyond the longest refractory period of 127 owing to pressure on the eyeball all the sinus beats were of normal configuration.

The above mentioned finding in Case 5 is similar to "pseudobradycardia dependent" BBB alternans observed in recently reported cases of Cohen and colleagues[7] in which a change from alternans to persistent BBB occurred as the cycle lengthened. However the disappearance of BBB with further increase of the CL proved the tachycardia dependence of the conduction defect. The phenomenon in their cases was also explained by a transition from a bidirectional 2:1 block into a sustained unidirectional block in a bundle branch. However, unidirectional block postulated by them was not "true" unidirectional block, namely they postulated that the bundle branch refractory period for the retrograde impulse was equal in length to that for the anterograde impulse.

In Case 5 in the present report paroxysmal supraventricular tachycardia occasionally occurred in which the CL was a period of 34 and all the beats were of right BBB configuration. It seems that although 2:1 retrograde block at the site of RDBBB occurred here all the anterograde impulses fell in the refractory period because the sum of two cycle lengths (i.e., a period of 68) is much shorter than the refractory period for the anterograde impulse. This indicates unidirectional block alternating with bidirectional block as illustrated by the diagram below the early portion of the top strip of Fig. 5. Recently the presence of 2:1 block in the ventricular conduction system was suggested in concealed bigeminy[8] and intermittent parasystole.[9,10] Such 2:1 block and the above mentioned alternating unidirectional block appear to be governed by the same mechanism.

In the other cases in the present report when the CL was shorter than the critical CL inducing RDBBB the beat of a normal configuration could not be found even after exercise. The probable reason for this is that in these cases the



Fig 5 Case 5 Electrocardiogram after exercise in the same patient as in *Fig 4* The lower two strips are continuous *Thickly shaded areas* in the diagrams represent the refractory period for the retrogradely conducted impulse i e the period showing bidirectional block during which both the anterograde impulse and the retrograde impulse are blocked *Thinly shaded areas* represent the period showing unidirectional block during which the anterograde impulse is blocked but the retrograde impulse is conducted The deflection marked with *a* in the middle strip is an artifact Abbreviations are the same as in *Fig 1*

strip of Fig 1 In Case 1 the critical CL inducing RDBBB was a period of 91 as mentioned above This indicates that the refractory period of the right bundle branch (RBB) is the period of 91 In the middle strip of Fig 1, the sinus impulse labelled S_4 is blocked within the RBB because the preceding CL S_3 S_4 is shorter than the refractory period of the RBB However after a period of 6 from that time the sinus impulse S_4 conducted from the left bundle branch penetrates retrogradely into the blocked site of the RBB Consequently the subsequent sinus impulse S_5 is again blocked within the RBB despite the fact that the CL S_4 S_5 is longer than the refractory period of the RBB In the same way the subsequent sinus impulses S_6 and S_7 are blocked within the RBB in succession Thus retrograde conduction to the blocked RBB maintains RDBBB until the CL is prolonged beyond a period of 97 (i e, the RBB refractory period of 91 plus the period of 6) If the sinus impulse S_4 were not conducted retrogradely to the blocked RBB the subsequent sinus impulse S_5 would not be blocked within the RBB and as a result RDBBB would not be maintained Moe Mendez and Han[8] demonstrated experimentally that functional bundle branch block was maintained owing to such repeated retrograde conduction The feature mentioned above does not indicate true 'unidirectional block, namely this can be explained without any difference between the refractory period for the anterogradely conducted impulse and that for the retrogradely conducted impulse

However, even when the CL is shortened below the above mentioned refractory period of the RBB RDBBB is also maintained as shown in the bottom strip of Fig 1 Therefore, we must assume that even in such rapid rhythm retrograde conduction to the blocked RBB occurs in succession The relationship represented in Fig 2 suggests that the expected decrease in the refractory period with shortening of the preceding CL did not occur here In the recent electrophysiological study by Denes and colleagues[3] the same feature was also demonstrated in four of five patients with RDBBB These facts suggest that the RBB refractory period for the retrogradely conducted impulse is not equal in length to that for the anterogradely conducted impulse namely that the former is considerably shorter than the l

changes in the preceding CL the critical CL inducing RDBBB was invariable extending over two years In the other patients the critical CL inducing RDBBB varied within a comparatively short period However when RDBBB was maintained for only a few cycles the critical CI allowing reversion to normal conduction was always longer than the critical CL inducing RDBBB here in all patients except one In one patient such a distinct difference in CL could not be disclosed because the critical CL inducing RDBBB varied from cycle to cycle

These observations suggest that independent of variations in the refractory period of the blocked bundle branch the critical CL allowing reversion to normal conduction was considerably longer than this refractory period in all patients The possible mechanisms by which RDBBB could be maintained are discussed The most probable mechanism appears to be true unidirectional block in the affected bundle branch in which the refractory period for the retrogradely conducted impulse is shorter than that for the anterogradely conducted impulse

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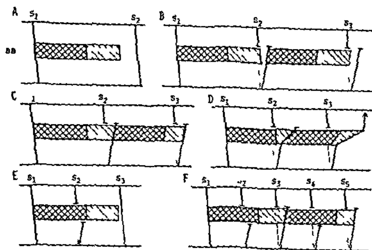


Fig 6 Diagrams to illustrate the relationship between the cycle length and the impulse conduction in rate dependent bundle branch block *Thickly shaded areas* represent the refractory period for the retrogradely conducted impulse *Thinly shaded areas* represent the period showing unidirectional block Impulse conduction in the affected bundle branch is represented *by solid lines* whereas impulse conduction in the contralateral bundle branch is represented *by dashed lines* *BB* = bundle branch *S* = sinus impulse

CL would not be shortened below the refractory period for the retrograde impulse

In conclusion, "true unidirectional block in the affected bundle branch appears to be the most probable mechanism by which RDBBB can be maintained Diagrams in Fig 6 illustrate the relationship between the CL and the conduction of the anterograde and retrograde impulses at the site of RDBBB Thickly shaded areas in the diagrams represent the refractory period for the retrograde impulse (RPR), i e the period showing bidirectional block, during which both the anterograde impulse and the retrograde impulse are blocked Thinly shaded areas represent the period showing unidirectional block during which the anterograde impulse is blocked but the retrograde impulse is conducted The sum of the periods of bidirectional and unidirectional block corresponds to the refractory period for the anterograde impulse (RPA)

Diagram A in Fig 6 indicates that when the CL S_1 S following normal conduction is longer than the RPA the anterograde impulse S passes through the bundle branch

Diagram B shows that when the CL S_1 S is slightly shorter than the RPA the anterograde impulse S is blocked within the bundle branch After some delay the retrograde impulse is conducted to the blocked bundle branch Here the retrograde impulse falls after the RPA Thus when the subsequent cycle lengths (including the CL S S_3) are slightly longer than the RPA bundle branch block is maintained because of repeated retrograde conduction However, this does not indicate true unidirectional block, namely, the feature shown in diagram B can be explained without any difference in length between the RPA and the RPR

Diagram C indicates that even when the cycle lengths S_1-S and S S_3 are both shorter than the RPA the retrograde impulses S and S_3 are conducted to the blocked bundle branch in succession because these impulses fall in the period of unidirectional block Thus, RDBBB can be maintained for a long time

Diagram D shows that when the retrograde impulse falls in the period of unidirectional block shortly after the RPR its conduction time within the bundle branch may be markedly prolonged in some cases If such a retrograde impulse falls after the refractory period in the region above the site of RDBBB this impulse may possibly re enter the ventricles after passing through the contralateral bundle branch although in the cases in the present report such re entrant extrasystoles were not found In my recently reported case of intermittent ventricular parasystole [11] the presence of re entrant ventricular extrasystoles due to a similar mechanism was demonstrated

Diagram E demonstrates that when the retrograde impulse S falls in the RPR but the sum of the cycle lengths S_1 S_2 and S_2 S_3 is longer than the RPA the anterograde impulse S_3 passes through the bundle branch despite the fact that these cycle lengths are both far shorter than the RPA

Diagram F shows that when the CL is further shortened the anterograde impulses S_3 and S_5 fall in the RPA Thus bundle branch block is again maintained as the result of 2 1 retrograde conduction In cases in which the RPR is considerably shorter than one half of the RPA whenever the retrograde impulse falls in the RPR the subsequent anterograde impulse will fall in the RPA In such cases therefore when the CL is shorter than the RPA, the anterograde impulse is always blocked within the bundle branch whether the retrograde impulse is blocked or not

Summary

In five patients with tachycardic RDBBB (rate dependent bundle branch block) variations in the critical CL (cycle length) inducing RDBBB were investigated In one patient independent of

changes in the preceding CL the critical CL inducing RDBBB was invariable extending over two years In the other patients the critical CL inducing RDBBB varied within a comparatively short period However when RDBBB was maintained for only a few cycles the critical CL allowing reversion to normal conduction was always longer than the critical CL inducing RDBBB here in all patients except one In one patient such a distinct difference in CL could not be disclosed because the critical CL inducing RDBBB varied from cycle to cycle

These observations suggest that independent of variations in the refractory period of the blocked bundle branch the critical CL allowing reversion to normal conduction was considerably longer than the refractory period in all patients The possible mechanisms by which RDBBB could be maintained are discussed The most probable mechanism appears to be true unidirectional block in the affected bundle branch in which the refractory period for the retrogradely conducted impulse is shorter than that for the anterogradely conducted impulse

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Effects of bundle branch block on experimental A-V reentrant tachycardia

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Most cases of ventricular preexcitation reflect the presence of an anomalous A V pathway, which may be located in either the right or left A V rings, or within the atrioventricular septum [1 3] In patients with preexcitation, circus movement paroxysmal tachycardias (PSVT) usually involve the normal pathway as antegrade limb and anomalous pathway as retrograde limb [2 5] In patients with circus movements involving retro gradelv conducting anomalous pathways, it has been suggested that development of functional bundle branch block ipsilateral to the anomalous pathwav produces a slowing in the rate of parox ysmal tachycardia [6 10] It has been additionally suggested that the presence or absence of this slowing during bundle branch block could be used as a diagnostic sign for lateralization of anoma lous pathways [6 12]

Recently Pritchett and co workers,[13] further elucidated this phenomenon They studied 15 patients with left free wall anomalous pathways, three patients with right free wall anomalous pathways and four patients with presumptive septal preexcitation Ventriculo atrial conduction times were increased during paroxysmal tachy cardia when functional bundle branch block occurred ipsilateral to the location of an anoma lous pathway Contralateral functional bundle branch block did not affect V A conduction during PSVT in these patients In patients with septal anomalous pathways, neither right or left bundle branch block appeared to affect V A conduction times during PSVT Since the occurrence and lateralization of functional bun dle branch block could not be controlled in the above study it was not possible to look at the effects of both right and left bundle branch in all patients

In the present studv we extend the observa tions of Prichett and colleagues[13] by systemati cally examining the effects of ipsilateral and contralateral bundle branch block on experi mented A V reentrant paroxysmal tachycardia in dogs The experimental model utilized an anom alous pathway simulator so that the effects of bundle branch block could be examined utilizing multiple anomalous pathway locations in the same dog

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Supported in part by National Institutes of Health grant HL18794 01 United States Public Health Service training grant HL 05879 06 Basic Institutional Support West Side Veterans Administration Hospital (MRIS No 1878) Veterans Administration grant 0363 01 and Chicago Heart Association grant A76 59 Chicago Illinois

Received for publication Oct 3 1977

Accepted for publication Nov 2 1977

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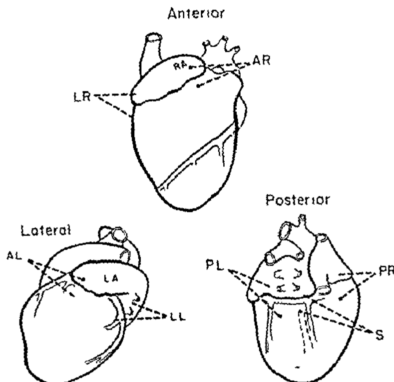


Fig 1 Schematic representation of the seven anomalous pathway locations. Anterior lateral, and posterior views of the heart are shown. Anomalous pathway locations both atrial and ventricular are represented by closed circles. *AR* = anterior right *LR* = lateral right *AL* = anterior left *LL* = left lateral *PL* = posterior left *S* = posterior septum *PR* = posterior right *RA* = right atrium *LA* = left atrium

Methods and materials

Seventeen mongrel dogs weighing from 14 to 21 kilograms were premedicated with morphine sulfate (2 mg /Kg intramuscularly) and anesthetized with Nembutal (30 mg /Kg intravenously). Ventilation was maintained with endotracheal intubation and a Harvard Respirator. Autonomic blockade was achieved by bilateral cervical vagotomy and propranolol administration (1 mg /Kg intravenously). The chest was opened through a midsternotomy and the heart suspended in a pericardial cradle.

Close pairs of plunge bipolar electrodes (Teflon coated stainless steel wires of 0 003 inch diameter) were positioned at seven contiguous atrial and ventricular sites around the A V ring in order to simulate the atrial and ventricular insertions of anomalous pathways. The following anomalous pathway sites were utilized (Fig 1) (1) anterior right (AR) at the right atrial appendage and underlying right ventricular outflow tract (2) posterior right (PR) at the posterior right atrium and contiguous right ventricle (just to the right of the intra atrial and intraventricular grooves) (3) lateral right (LR) at a midpoint between AR and PR (4) septum (S) at the posterior atrioventricular septum (the atrial septal site was reached by plunging electrodes through the posterior free wall of the right atrium and lodging them in the posterior septum—the corresponding ventricular septum was reached by plunging electrodes through the posterior interventricular septum and lodging them 1 to 2 cm deep in the posterior septum) (5) anterior left (AL) at the left atrial appendage and underlying left ventricle (6) posterior left (PL) at the posterior left atrium just above the coronary sinus and the adjacent left ventricle (7) left lateral (LL) at midpoint between AL and PL. Special attention was paid to positioning the electrodes close to the A V ring at a distance of 1 cm.

A 5F bipolar electrode catheter was introduced into the left carotid artery and advanced behind the non coronary cusp of the aortic valve for His bundle recordings[14] His bundle potentials were validated by atrial and His bundle pacing[14,15] Standard electrocardiographic Leads I II III His bundle electrograms right atrial electro

Table I Cycle length of A V reentrant PSVT with and without bundle branch block (mean ± SEM in msec)

AP site	Control (N = 7)	RBBB (N = 7)	P	Control (N = 10)	LBBB (N = 10)	P
AR	281 5 ± 8 3	318 ± 9 5	< 0 001	281 5 ± 7 4	281 ± 8	NS
LR	276 5 ± 9 4	303 ± 12	< 0 001	275 ± 9	274 ± 6 4	NS
PR	266 ± 8	289 ± 9 3	< 0 01	267 5 ± 5	261 ± 9	NS
S	271 ± 10 5	273 5 ± 11	NS	273 5 ± 8	278 ± 6 5	NS
PL	277 ± 11	276 ± 10	NS	275 ± 6 7	309 ± 6 3	< 0 001
LL	289 ± 10 5	285 ± 10	NS	269 ± 9	307 ± 7 7	< 0 01
AL	286 ± 10 5	286 5 ± 11	NS	280 ± 7 5	312 5 ± 7 6	< 0 001

Abbreviations AP = anomalous pathway RBBB = right bundle branch block LBBB = left bundle branch block AR = anterior right LR = lateral right PR = posterior right S = septum PL = posterior left LL = lateral left AL = anterior left NS = non significant P = P value

grams local ventricular electrograms and stimulus artifacts were simulataneously displayed on an oscilloscope and recorded on a multichannel recorder (Electronics for Medicine DR 8 White Plains, N Y) at paper speeds of 100 and 200 mm /sec

The electronic anomalous pathway simulator was schematically depicted in a previous publication [16] Local electrograms recorded from the ventricle were preamplified by a multichannel recorder and filtered and differentiated by input circuitry The resulting signal was used to trigger a crystal controlled digital timer programmable to a specific pathway delay between 1 and 999 msec When the preset time was reached the timer triggered a pulse generator adjusted to deliver an above threshold stimulus to the atrial stimulating electrodes Thus the relevant features of this anomalous pathway simulator include ability for ventricular sensing, retrograde conduction with programmable conduction time, and atrial stimulation

Experimental protocol

A V reentrant tachycardias were induced in each of the dog at all seven sites with a programmed anomalous pathway conduction time of 100 msec This conduction time was chosen since it allowed induction of paroxysmal tachycardia with a cycle length comparable to that seen in patients with Wolff Parkinson White syndrome and PSVT Recordings were obtained during each tachycardia at a paper speed of 100 mm /sec The following subintervals were measured (1) S A interval, from the stimulus artefact to the first high frequency electrogram of the low septal right atrium recorded from the His bundle recording catheter This interval reflected intra atrial conduction time from the atrial stimulation site to the low septal right atrium (2) A H interval, from the first high frequency deflection on the low septal right atrial electrogram to the His bundle electrogram This interval reflected A V nodal conduction time (3) H V_L interval from the His bundle electrogram to the first high frequency deflection of the local ventricular electrogram recorded from the tested ventricular sensing site This interval reflected conduction time from the His bundle to the sensing site (4) V_L S interval from the sensed ventricular electrogram to the stimulus artefact This interval was 100 msec reflecting programmed delay of the anomalous pathway simulator

After control values were obtained right bundle branch block was produced in seven of the dogs by inserting a needle through the right ventricular wall and traumatizing the second portion of the right bundle branch [1] Similarly in another group of 10 dogs left bundle branch block was induced by traumatizing the main left bundle branch with a needle introduced through the left ventricular wall at the apex of the heart [17] A V reentrant tachycardia was again induced in all dogs at all sites after a stable bundle branch block was produced Measurements of tachycardia cycle length and subintervals were determined

At the termination of each experiment the heart was excised and the exact location of the plunge wires were verified Lugol s solution was used to identify the intraventricular conducting system and to verify the interruption of the traumatized bundle branch

All the intervals given represent the average of

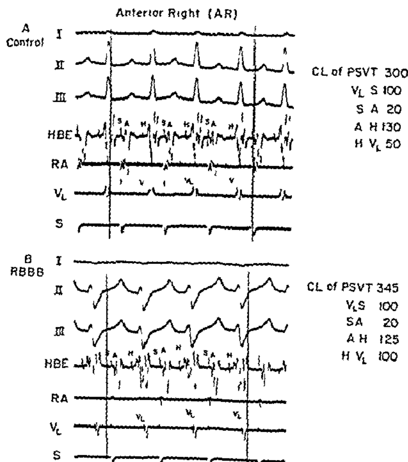


Fig 2 Induced A V reentrant tachycardia (PSVT) Representative example from the anterior right location before (*Panel A*) and after (*Panel B*) right bundle branch block was produced Shown are electrocardiographic Leads I II, III *HBE* = His bundle recordings *RA* = right atrial electrogram V_L = local ventricular electrogram *S* = stimulus artifact Paper speed is 100 mm /sec and time intervals are at 1 sec Values for the different components of the cycle length (*CL*) of supraventricular tachycardia before and after RBBB are shown *in the right column*

10 consecutive measurements Statistical analysis was performed using the Student t test for paired data and analysis of variance

Results

Cycle length of tachycardias (Table I) The effects of right bundle branch block on the cycle length of A V re-entrant tachycardias in seven dogs at all sites is presented in Table I Cycle length of tachycardias was significantly increased only with the three right sided anomalous pathway locations increasing by a mean of 37 ± 3 msec ($P < 001$) with the anterior right site by 27 ± 3 msec ($P < 001$) with the lateral right site and by 23 ± 4 msec ($P < 01$) with the posterior right site Cycle length of tachycardias utilizing septal and left sided pathways were not significantly changed Fig 2 is a representative example of one of the experiments conducted with an anterior right anomalous pathway

The effects of left bundle branch block on the cycle length of A V re-entrant tachycardias in 10 dogs at all sites is presented in Table I After left bundle branch block cycle length of PSVT was significantly increased only with the three left sided pathway locations increasing by a mean of 34 ± 2 6 msec ($P < 001$) with the posterior left site by 38 ± 4 6 msec ($P < 01$) with the left lateral site and by 32 5 ± 3 3 msec ($P < 001$) with the anterior left site Cycle length of tachycardias utilizing septal and right sided locations were not significantly changed Fig 3 is a representative example of one of the experiments conducted with a left lateral anomalous pathway

Subintervals The cycle length of A V reen

Table I Cycle length of A V reentrant PSVT with and without bundle branch block (mean ± SEM in msec)

AP site	Control (N = 7)	RBBB (N = 7)	P	Control (N = 10)	LBBB (N = 10)	P
AR	281 5 ± 8 3	318 ± 9 5	< 0 001	281 5 ± 7 4	281 ± 8	NS
LR	276 5 ± 9 4	303 ± 12	< 0 001	275 ± 9	274 ± 6 4	NS
PR	266 ± 8	289 ± 9 3	< 0 01	267 5 ± 5	261 ± 9	NS
S	271 ± 10 5	273 5 ± 11	NS	273 5 ± 8	278 ± 6 5	NS
PL	277 ± 11	276 ± 10	NS	275 ± 6 7	309 ± 6 3	< 0 001
LL	289 ± 10 5	285 ± 10	NS	269 ± 9	307 ± 7 7	< 0 01
AI	286 ± 10 5	286 5 ± 11	NS	280 ± 7 5	312 5 ± 7 6	< 0 001

Abbreviations AP = anomalous pathway RBBB = right bundle branch block LBBB = left bundle branch block AR = anterior right LR = lateral right PR = posterior right S = septum PL = posterior left LL = lateral left AL = anterior left NS = non significant P = P value

grams, local ventricular electrograms and stimulus artifacts were simulataneously displayed on an oscilloscope and recorded on a multichannel recorder (Electronics for Medicine DR 8 White Plains N Y) at paper speeds of 100 and 200 mm/sec

The electronic anomalous pathway simulator was schematically depicted in a previous publication [16] Local electrograms recorded from the ventricle were preamplified by a multichannel recorder, and filtered and differentiated by input circuitry The resulting signal was used to trigger a crystal controlled digital timer, programmable to a specific pathway delay between 1 and 999 msec When the preset time was reached the timer triggered a pulse generator adjusted to deliver an above threshold stimulus to the atrial stimulating electrodes Thus, the relevant features of this anomalous pathway simulator include ability for ventricular sensing retrograde conduction with programmable conduction time and atrial stimulation

Experimental protocol

A V reentrant tachycardias were induced in each of the dogs at all seven sites with a programmed anomalous pathway conduction time of 100 msec This conduction time was chosen since it allowed induction of paroxysmal tachycardia with a cycle length comparable to that seen in patients with Wolff Parkinson White syndrome and PSVT Recordings were obtained during each tachycardia at a paper speed of 100 mm/sec The following subintervals were measured (1) S A interval from the stimulus artefact to the first high frequency electrogram of the low septal right atrium recorded from the His bundle recording catheter This interval reflected intra atrial conduction time from the atrial stimulation site to the low septal right atrium (2) A H interval from the first high frequency deflection on the low septal right atrial electrogram to the His bundle electrogram This interval reflected A V nodal conduction time (3) H V_t interval from the His bundle electrogram to the first high frequency deflection of the local ventricular electrogram recorded from the tested ventricular sensing site This interval reflected conduction time from the His bundle to the sensing site (4) V_t S interval from the sensed ventricular electrogram to the stimulus artefact This interval was 100 msec reflecting programmed delay of the anomalous pathway simulator

After control values were obtained right bundle branch block was produced in seven of the dogs by inserting a needle through the right ventricular wall and traumatizing the second portion of the right bundle branch [17] Similarly in another group of 10 dogs left bundle branch block was induced by traumatizing the main left bundle branch with a needle introduced through the left ventricular wall at the apex of the heart [17] A V reentrant tachycardia was again induced in all dogs at all sites after a stable bundle branch block was produced Measurements of tachycardia cycle length and subintervals were determined

At the termination of each experiment the heart was excised and the exact location of the plunge wires were verified Lugol s solution was used to identify the intraventricular conducting system and to verify the interruption of the traumatized bundle branch

All the intervals given represent the average of

Table II H V_L during PSVT with and without bundle branch block (mean ± SEM in msec)

AP site	Control (N = 7)	RBBB (N = 7)	P	Control (N = 10)	LBBB (N = 10)	P
AR	39.5 ± 3	87 ± 3	< 0.001	37.5 ± 2.4	37 ± 2.5	NS
LR	37 ± 2.4	69 ± 5	< 0.001	34.5 ± 2	35 ± 2	NS
PR	40 ± 2.4	63 ± 4.7	< 0.001	38 ± 3	38 ± 2.6	NS
S	40 ± 2.7	43.5 ± 4.6	NS	37.5 ± 3	42.5 ± 5	NS
PL	37 ± 1.5	43 ± 1.8	NS	35.5 ± 3	85.5 ± 5	< 0.001
LL	41 ± 3.5	48 ± 3.4	NS	38 ± 2	80 ± 2.6	< 0.01
AL	40 ± 3	36.5 ± 7	NS	36.5 ± 2.5	79 ± 3.6	< 0.001

Abbreviations AP = anomalous pathway RBBB = right bundle branch block LBBB = left bundle b anch block NS = non signifi nt P = P value

sites With left bundle branch block A H decreased by 12 ± 5 msec ($P < 0.05$) 15 ± 5 msec ($P < 0.05$) and 13 ± 4 msec ($P < 0.05$) with tachycardias respectively utilizing the left posterior lateral and anterior sites S A intervals did not change significantly after either right or left bundle branch block

Discussion

In patients with preexcitation A V reentrant tachycardias (PSVT) usually reflect circus move ment with the normal pathway as antegrade limb and the anomalous pathway as retrograde limb[2,3] The cycle length of the tachycardia is determined by A V nodal conduction time His Purkinje conduction time conduction through ventricular muscle anomalous pathway conduc tion and intra atrial conduction

It has been suggested that the development of functional bundle branch block during PSVT ipsilateral to the location of an anomalous pathway results in lengthening of the cycle length of PSVT[4] This lengthening is thought to be due to an increase in the size of the reentrant pathway by addition of transseptal conduction time Coumel and associates has suggested that the presence or absence of this lengthening in cycle length could be used as a sign for lateralization of anomalous pathway location Thus in 1972 Coumel and Waynberger[6] reported a patient with left ventricular preexcitation and A V reentrant PSVT in whom the development of functional left bundle branch block was accompanied by an increase in PSVT cycle length of 20 msec PSVT cycle length was not changed by functional right bundle branch block This observation was later corroborated by other reports from Slama Coumel and Bouvrain[7] in 1973 Coumel and Attuel[8] in 1974 Spurrell and colleagues in 1974 and Neuss and Schlepper in 1975 This phenom enon has also been used to predict and locate concealed retrogradely conducting anomalous pathways

More recently Pritchett and co workers[3] have extended these observations by analyzing the changes in V A conduction during episodes of A V reentrant paroxysmal tachycardia when func tional bundle branch block develops They reported 15 patients with left free wall anomalous pathways three patients with right free wall anomalous pathways and four patients with septal preexcitation Ventriculo atrial conduction times were prolonged during A V reentrant tachycardia when functional bundle branch block developed ipsilateral to the location of an anom alous pathway Functional bundle branch block contralateral to anomalous pathway did not prolong V A time In patients with septal anoma lous pathways neither bundle branch block altered V A time during PSVT

Our results substantiated these clinical obser vations We utilized a canine model of preexcita tion with an anomalous pathway simulator char acterized by unidirectional conduction (ventric ulo atrial) programmable conduction time and predetermined location along the A V ring A V reentrant tachycardias were easily induced using the normal pathway for antegrade conduction and the anomalous pathway (simulator) for retrograde conduction Following experimentally induced bundle branch block ipsilateral to anom alous pathway locations cycle length of A V reentrant PSVT was significantly increased With experimental bundle branch block contralateral to anomalous pathway location cycle length of PSVT was not changed Cycle length of PSVT utilizing septal anomalous pathways was not changed by either right or left bundle branch block

To further understand these results one can

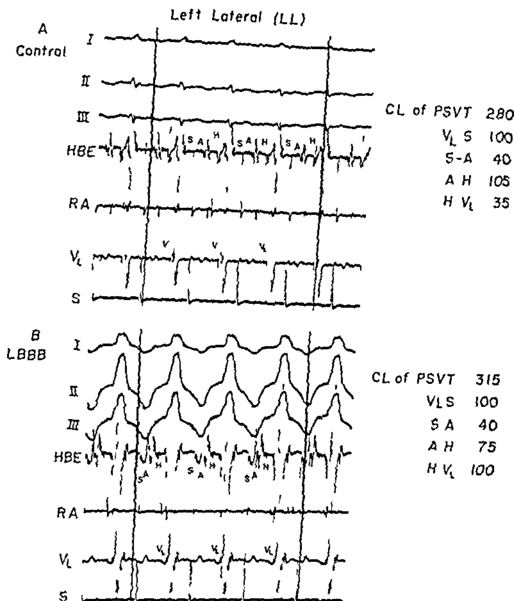


Fig 3 Induced A V reentrant tachycardia Representative example from the left lateral location before (*Panel A*) and after (*Panel B*) left bundle branch block was produced Values for the different components of the cycle length of PSVT are shown *in the right column*

trant PSVT in these experiments is the sum of the following subintervals S A A H H V_L and anomalous pathway delay (V_L S) Any significant change in cycle length of PSVT should be explainable on the basis of changes in subintervals

Mean H V_L intervals during tachycardia before and after right and left bundle branch block are presented in Table II With right bundle branch block, H V_L interval significantly increased with tachycardia utilizing the three right sites H V_L increased by a mean of 48 ± 2 4 msec with the anterior right location (P < 001) by a mean of 32 ± 4 msec with the lateral right (P < 001) and by a mean of 23 ± 4 msec with the posterior right location (P < 001) There was no significant differences in H V_L with septal and left sites With left bundle branch block H V_L interval was significantly increased with tachycardia utilizing the three left sided sites Thus, H V_L increased by a mean of 50 ± 4 6 msec with the posterior left location (P < 001), by a mean of 42 ± 5 msec in the left lateral (P < 001) and by 42 5 ± 5 msec in the anterior left (P < 001) His Purkinje conduction time (conventional H V interval) was not altered by either right or left bundle branch block Therefore the changes in H V_L represented increases in intraventricular conduction time

There were compensatory decreases in A H intervals for the increases in H V_L with bundle branch block occurring ipsilateral to anomalous pathway location Thus with right bundle branch block A H decreased by 8 5 ± 3 2 msec (P < 0 05) 14 ± 2 6 msec (P < 0 05) and 8 ± 2 6 msec (P < 0 05) with tachycardias respectively utilizing the right anterior lateral and posterior

Summary

The effects of bundle branch block on experimental A V reentrant tachycardia (PSVT) were studied in 17 dogs using an anomalous pathway simulator (APS) The APS was a programmable digital electronic circuit with ability for ventricular sensing retrograde conduction with programmable conduction time and atrial stimulation Close bipolar electrodes were positioned at seven contiguous atrial and ventricular sites (V_L) along the A V ring these being anterior lateral and posterior right (AR LR PR) septal (S) and posterior lateral and anterior left (PL LL AL) Right (R) (seven dogs) and left (L) (10 dogs) bundle branch block (BBB) were produced with transcardiac needle After BBB cycle length (CL) of A V reentrant PSVT was significantly increased only with ipsilateral sites Thus with RBBB CL of PSVT increased by 37 ± 3 msec 27 ± 3 msec and 23 ± 4 msec ($P < 0.001$) at AR LR and PR sites respectively With LBBB CL of PSVT increased only with left sided sites Thus CL increased by 34 ± 2.6 msec 38 ± 4.6 msec and 32 ± 3.3 msec ($P < 0.001$) with PL LL and AL sites respectively PSVT CL and septal site did not change significantly after either R or LBBB The increase in CL was explicable in terms of corresponding increases in intraventricular conduction time ($H V_L$) There were slight compensatory decreases in A H intervals for the increases in $H V_L$ These studies confirm findings suggested by clinical electrophysiological observation

We are indebted to Ms *Lore U Foley* for her secretarial assistance

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look at the determinants of PSVT cycle length with our experimental model PSVT cycle lengths equals the sum of the following subintervals (1) S A, conduction time from the atrial stimulating electrode to the low septal right atrium (from His bundle catheter) This was a function of anomalous pathway atrial site and independant of cycle length This was unchanged by experimental bundle branch block (2) A H, from low septal right atrium to the His bundle electrogram, a measure of A V nodal conduction time This was partially a function of conduction times in the rest of the circuit (3) H V_I, from His bundle electrogram to the onset of the ventricular electrogram at the ventricular sensing electrode (close to the A V ring) This was a function of ventricular site and independent of cycle length H V_L encompassed H V (from His bundle electrogram to the onset of ventricular activation), and V V_L conduction time from onset of ventricular activation to the ventricular sensing site (4) V_L S from ventricular sensing site to the atrial stimulus This was a programmed function in this series of experiments and was 100 msec

In these experiments bundle branch block ipsilateral to an anomalous pathway location significantly increased H V_I during PSVT Contralateral bundle branch block had no significant effect When analyzed, it was demonstrated that the increase in H V_I, reflected an increase in V V_L and not H V The lack of change in H V was consistant with prior experimental work which demonstrated that conduction times in both bundle branches to the onset of ventricular activation in the ipsilateral chamber were essentially equal [18,20] The increase in V V_I with bundle branch block ipsilateral to an anomalous pathway reflected change in sequence of ventricular activation Ventricular activation was initiated in the contralateral ventricle proceeded across the ventricular septum and then invaded the ipsilateral ventricle The change in V V_L with bundle branch block ipsilateral to an anomalous pathway thus reflected primarily the addition of transseptal conduction time With bundle branch block contralateral to an anomalous pathway the activation sequence of the ventricle with the anomalous pathway was essentially unchanged since its bundle branch was intact, resulting in no change in V V_L

The magnitude of increase of V V_L with ipsilateral bundle branch block during PSVT was similar for both right bundle branch block (range of 23 to 48 msec) and left bundle branch block (range of 42 to 50 msec) It is interesting to note that our values correlated very closely with calculated transseptal conduction times of 40 msec reported in dogs by Lewis and Rothschild [1] and of 30 to 40 msec as reported by Wilson and Hermann [27] in 1920, and of 40 msec reported by Rodriquez and Sodi Pallares [4] in 1952

The failure of H V_L (and of necessity V V_L) to increase cycle length of PSVT with septal anomalous pathways suggested that the septal location (postero basal) sensed ventricular activation arriving simultaneously from both ventricles, so that delay in the input of one or the other ventricle did not increase V V_L This is presumably the reason for the clinically observed failure of bundle branch block to increase V A conduction time, during spontaneous PSVT in patients with septal anomalous pathway

In previous work[16] utilizing the anomalous pathway simulator, we demonstrated that A H interval was a function of programmed anomalous pathway delay (V_L S) As programmed V_L S was decreased, A H increased This reflected a compensatory increase in A V nodal conduction time, as the cycle length of PSVT was decreased due to the decrease in V_L S In the present study the decrease in A H during PSVT with bundle branch block ipsilateral to anomalous pathway site was compensatory for the increase in V V_L, which presented itself to the A V node as a total increase in retrograde conduction time (increase of H V_I with a fixed V_I S of 100 msec) The decrease in A H was of small enough magnitude, so that it only partially offset the increase in H V_I with resultant increase in cycle length of PSVT with ipsilateral bundle branch block

Although in our experimental model increase in intraventricular conduction time was responsible for the slowing in cycle length of PSVT it is worth emphasizing that in patients with PSVT and functional bundle branch block a detailed analysis of subintervals is necessary [13] For instance it is possible that the decrease of A H might be of such magnitude to completely offset the lengthening in ventriculo atrial conduction time resulting in no change in cycle length of PSVT Changes in H V might also occur with functional bundle branch block complicating PSVT in patients [11]

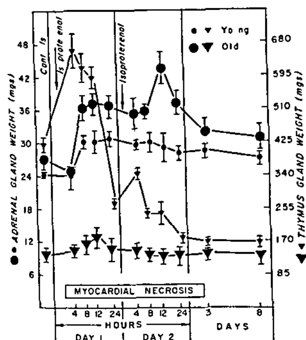


Fig 1 Changes in adrenal and thymus gland weight of young vs old Sprague Dawley rats subjected to an acute myocardial infarction by two subcutaneous injections of isoproterenol and autopsied at regular intervals during Days 1 and 2 while myocardial necrosis is on going on Day 3 when myocardial necrosis reaches a zenith and on Day 8 when myocardial repair is essentially complete *Each point depicted* represents the Mean ± Standard Error *n = 24* for each of the control groups *n = 6* for each of the experimental groups The same protocol was followed in *Figs 2* through 7

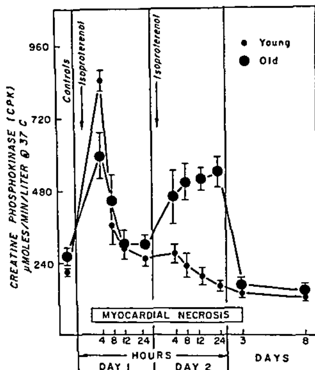


Fig 2 Changes in serum creatine phosphokinase *(SCPK)*

chandes PAS stain for glycoprotein von Kossa stain for calcium Verhoeff van Gieson stain for elastic tissue and frozen sections cut at 10 μm were stained with Sudan black B for lipids

The data was evaluated statistically by analysis of variance and Student s t test according to the statistical methods and tables cited by Snedecor

Results

General observations Young and old male rats subjected to an isoproterenol induced myocardial infarction exhibited the characteristic sequence of readily observable changes and signs of shock which have been described in detail Within minutes of receiving the isoproterenol young and old rats exhibited tachycardia dyspnea anuria and prostration

Survival Four hours after the first injection of isoproterenol all of the young males survived while 81 per cent of the old males survived Twenty four hours later 86 per cent of the young and 76 per cent of the old animals remained alive

On Day 2 the same syndrome of anuria and prostration observed on Day 1 was promptly re established after the administration of isoproterenol All of the young males survived while only 60 per cent of the old males survived By Day 3 however survival of the old males increased to 83 per cent despite the fact that myocardial infarction was most severe on this day By Day 8 when both gross and histopathologic evidence indicated that the myocardium had undergone repair survival of old males had increased to 100 per cent

Gravimetric observations

Changes in heart weight The average body weight of the 15 month old males ranged from 150 to 200 grams more than their young male counterparts and concomitantly their hearts were substantially heavier than the young rats The absolute weight (as well as the ratio of heart weight to body weight) of both the young and old rats increased appreciably within 4 hours after the first injection of isoproterenol The heart weights of the young and old rats continued to

Snedecor G W Statistic l m thods, 6th ed Cedar Falls Iowa, 1967 Iowa State College Press

Myocardial infarction in young vs old male rats Pathophysiologic changes

Bernard C Wexler, Ph D
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For several years, we have been investigating the induction of acute myocardial infarction in rats by means of the potent beta adrenergic stimulating agent, isoproterenol[1-8] The pathophysiologic changes in these animals during the acute phases of myocardial necrosis and repair mimic those which occur in patients, e g, changes in serum enzymes lipids, catecholamines steroids, etc In earlier investigations we had also demonstrated definite electrocardiographic evidence of myocardial ischemia in isoproterenol treated rats[8] By regulating the dose of isoproterenol, we can induce a myocardial infarct of equal size and severity in young and old rats In this report we describe the salient pathophysiologic differences between young and old rats during acute myocardial infarction

Materials and methods

A total of 400 adult male Sprague Dawley rats were used in these investigations 200 young males, 90 days of age, weighing 310 to 350 grams, and 200 old males, 15 months of age, weighing 500 to 580 grams * Both young and old rats were injected subcutaneously with isoproterenol at a dose level of 50 mg per 100 grams of body weight (Day 1) A representative number of animals were killed 4, 8, 12 and 24 hours after the first injection On the following day (Day 2), the second injection of isoproterenol (same dose) was given and animals were killed 4, 8, 12, and 24 hours later On Day 3, 24 hours after the second injection of isoproterenol had been given and when myocardial necrosis reaches a zenith, two additional groups of young and old rats were killed On the eighth day after the first injection of isoproterenol (Day 8) when myocardial repair is usually completed, the remaining young and old isoproterenol treated rats were killed Two groups of young and old rats (injected with 0 9 per cent saline) served as baseline controls The sequential temporal autopsies provided us with a dynamic analysis of the pathophysiologic changes that occur in young vs old rats during acute myocardial infarction

Blood was withdrawn from the abdominal aorta of each animal by means of a heparinized syringe Plasma was separated by refrigerated centrifugation and analyzed by automated methods in our Auto Analyzer (Technicon) i e creatine phosphokinase (CPK) transaminases (SGOT, SGPT) lactic dehydrogenase (LDH) triglycerides free fatty acids total cholesterol glucose and blood urea nitrogen (BUN) * Circulating corticosterone (Compound B) levels were measured by the fluorometric method of Guillemin and associates[9] as an index of adrenal secretory activity Total myocardial hexosamine as an index of cardiac mucopolysaccharide content was analyzed by the method of Boas[1]

For histopathologic analyses organs and tissues were embedded in paraffin sectioned at 3 μm and stained with Hematoxylin and Eosin for routine examination Hale stain for mucopolysac

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Supported in part by grants from the Southwestern Ohio Heart Association the National Institute on Aging (AG 58?) and the National Heart Lung and Blood Institute (HL-21418) N I H

Received for publication Oct 10 1977

Accepted for publication Nov 7 1977

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The authors wish to express their gratitude to Mr Charles E Rast General Manager ARS/Sprague Dawley Madison Wisc for graciously providing the old male rats used in this investigation

*All of these automated procedures are detailed in the manual published by the Technicon Co *Automation in analytical chemistry* Technicon Mediad Inc New York

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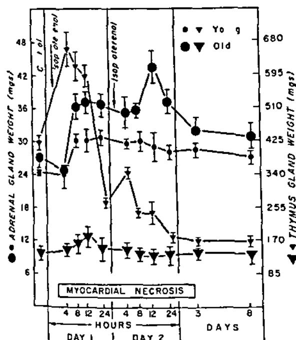


Fig 1 Changes in adrenal and thymus gland weight of young vs old, Sprague Dawley rats subjected to an acute myocardial infarction by two subcutaneous injections of isoproterenol and autopsied at regular intervals during Days 1 and 2 while myocardial necrosis is on going on Day 3 when myocardial necrosis reaches a zenith, and on Day 8 when myocardial repair is essentially complete *Each point depicted* represents the Mean ± Standard Error $n = 24$ for each of the control groups $n = 6$ for each of the experimental groups The same protocol was followed in *Figs* 2 through 7

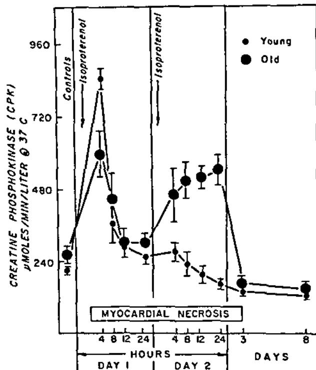


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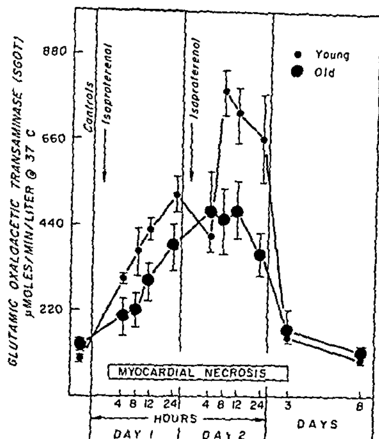


Fig 3 Changes in serum glutamic oxaloacetic transaminase (SGOT)

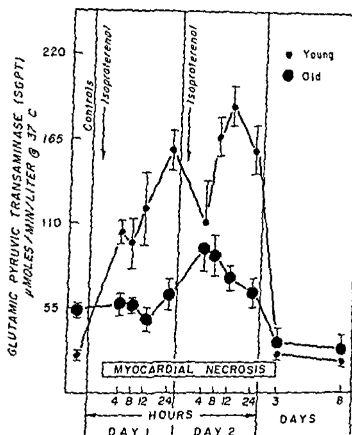


Fig 4 Changes in serum glutamic pyruvic transaminase (SGPT)

rise on Day 1 On Day 2 when cardiac necrosis and interstitial edema become manifest, the hearts of both the young and old rats continued to show a dynamic increase in weight the young rats exhibited the most sustained and greatest increase in absolute weight ($p < 0.001$) After 8 days although gross and histopathologic evidence indicated that the heart damage was repaired the absolute heart weight of the young and old rats remained above normal The dynamic changes in heart weight in young vs old rats are essentially identical to those already described in this journal [8]

Changes in adrenal and thymus gland weights The weight of the adrenal and thymus glands also underwent dynamic changes Both the young and old rats manifested an acute increase in adrenal size on Day 1 and an even greater increase on Day 2 remaining enlarged throughout the period of acute myocardial infarction and repair (Fig 1) Analysis of variance demonstrated a statistically significant over all greater increase in the adrenal weight of the old rats Despite the stress of acute myocardial infarction initially the thymus glands of the young rats increased in size and weight and then became progressively involuted (Fig 1) concomitant with increased adrenal size and increased adrenocortical activity (see below)

The thymus glands of the old rats which were naturally involuted at the outset, manifested none of the dynamic changes exhibited by their young counterparts (Fig 1)

Kidney weight The kidneys of the old rats were considerably heavier than the young rats i e 1 685 ± 12 mg vs 1 227 ± 8 mg Despite initial anuria (Days 1 and 2) followed by copious diuresis (Days 3 to 5) there were no dynamic or statistically significant changes in the weight of the kidneys of either the young or old rats

Congestive heart failure Using hydrothorax i e amount of fluid aspirated from the chest cage as an index of the severity of congestive heart failure we found that the old animals manifested much more severe failure than the young animals e g an average of 4 c c of chest fluid in young rats vs 8 c c in old rats The old rats manifested persistent anuria and 1 to 2 c c of chest fluid until Day 6 after which the anuria and hydrothorax were subsequently relieved young rats began to diurese copiously on Day 3 with virtually complete clearance of chest fluid by Day 5

Blood chemistry

Enzymes

Creatine phosphokinase (CPK) During the acute necrosis phase CPK levels rose steeply to a

peak level in both young and old rats as early as 4 hours after the first injection of isoproterenol and then promptly declined almost to normal levels (Fig 2) Following the second injection of isopro terenol CPK levels rose again in the old but not in the young rats CPK levels were normal throughout the myocardial repair phase i e Days 3 to 8 (Fig 2)

Glutamic oxaloacetic transaminase (SGOT) SGOT levels rose markedly in both the young and old rats during the acute necrosis phase of myocardial infarction (Fig 3) The young rats exhibited a steeper rise and higher levels than their older counterparts returning to normal levels during the repair phase

Glutamic pyruvic transaminase (SGPT) SGPT levels rose steeply and significantly ($p < 0.001$) in the young rats during the acute stages of cardiac necrosis and returned to normal during the myocardial repair phase (Fig 4) The older rats exhibited much less SGPT activity during this same period (Fig 4)

Lactic dehydrogenase (LDH) Young and old rats displayed an acute and marked increase in LDH LDH reached a zenith in young males 4 to 12 hours after the first injection of isoproterenol then decreased only to rise again after the second injection of isoproterenol LDH levels remained elevated in the older rats on Days 1 and 2 (Fig 5) LDH levels returned to normal in the young and old rats during the repair phase (Days 4 through 8)

Lipids

Triglycerides Changes in serum triglyceride levels occurred in opposite directions in young vs old rats (Table I) After a delayed rise young rats displayed elevated levels of serum triglycerides during the acute stages of cardiac necrosis and repair (Days 3 to 8) after an acute rise triglycer ide levels progressively decreased in old rats during this same period (Table I)

Free fatty acids Free fatty acids became acutely elevated in both young and old rats much more so in the young rats (Table I) However the free fatty acid levels in the young rats promptly returned to normal and remained so throughout the experiment whereas the free fatty acid levels in the old rats remained well above normal ($p < 0.001$) (Table I)

Total cholesterol Prior to treatment the older rats had considerably higher ($p < 0.001$) blood cholesterol levels than their young brothers (Table I) Circulating cholesterol levels rose in

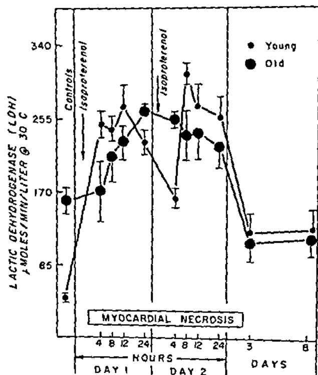


Fig 5 Changes in serum lactic dehydrogenase (*SLDH*)

both young and old rats on Day 1 remained slightly elevated in the young rats but were reduced to subnormal levels in the old rats ($p < 0.001$)

Glucose Acute and transitory hyperglycemia occurred in both the young and old rats i e on Day 1 in the old and Day 2 in the young (Table I)

Blood urea nitrogen (BUN) The young animals showed an abrupt increase in BUN levels during the acute myocardial necrosis phase on Days 1 and 2 (Table I) The old rats which had elevated BUN levels at the outset manifested a greater increase in their BUN levels in response to the stress of acute myocardial necrosis (Table I)

Adrenal steroids

Corticosterone (Compound B) Prior to treat ment the Compound B levels of the old rats were double those of the young rats During the first day of acute myocardial necrosis the old rats showed only a slight increase in circulating Compound B levels returning to normal levels for the duration of the experiment (Fig 6) The young animals manifested an initial drop in circu lating Compound B levels (Day 1) followed by a progressive and super normal increase in Com pound B levels (Day 2) ($p < 0.001$) reaching a

Table I Changes in serum lipids, glucose and blood urea nitrogen in young vs old male Sprague Dawley rats during the acute necrosis and repair phases of an isoproterenol induced myocardial infarction

	Triglyc (mg %)	*Free fatty acids mEq /L*	*Total chol (mg %)*	*Glucose (mg %)*	*B U.N (mg %)*
Young rats					
Controls	59 ± 4 (12)	538 ± 85 (10)	39 ± 5 (11)	165 ± 8 (11)	23 ± 06 (11)
Day 1 Isoproterenol 1st inj					
4 hours later	52 ± 4 (5)	1097 ± 105* (6)	40 ± 6 (5)	157 ± 6 (5)	27 ± 68 (5)
8 hours later	58 ± 7 (6)	423 ± 49 (5)	47 ± 5 (6)	155 ± 7 (6)	36 ± 48 (6)
12 hours later	87 ± 6 * (5)	528 ± 35 (5)	77 ± 5* (5)	138 ± 10** (5)	31 ± 48 (5)
24 hours later	132 ± 3* (6)	506 ± 30 (6)	60 ± 3** (6)	143 ± 5** (6)	34 ± 56 (6)
Day 2 Isoproterenol 2nd inj					
4 hours later	117 ± 9* (5)	611 ± 41 (5)	62 ± 3 (5)	295 ± 21* (6)	27 ± 2.3 (6)
8 hours later	115 ± 10 (6)	611 ± 50 (6)	55 ± 6 (6)	2[illegible]3 ± 36 (6)	31 ± 47 * (6)
12 hours later	95 ± 5* (5)	377 ± 42* (5)	50 ± 4 (5)	149 ± 5** (5)	37 ± 28 (5)
24 hours later	120 ± 7* (6)	470 ± 38 (6)	77 ± 8* (6)	148 ± 6* (6)	33 ± 63** (6)
Day 3	102 ± 8* (6)	294 ± 42 (6)	56 ± 4 (6)	134 ± 3* (6)	21 ± 10 (6)
Day 8	77 ± 8 (6)	338 ± 21* (6)	43 ± 5 (6)	156 ± 5 (6)	22 ± 09 (6)
Old Rats					
Controls	136 ± 16 (12)	199 ± 12 (12	109 ± 11 (11)	149 ± 7 (12)	27 ± 31 (11)
Day 1 Isoproterenol 1st inj					
4 hours later	195 ± 25 (6)	549 ± 69 (6)	96 ± 16 (6)	212 ± 15 (6)	27 ± 05 (6)
8 hours later	162 ± 24* (6)	419 ± 57 (6)	115 ± 14 (6)	209 ± 15 (6)	27 ± 10 (6)
12 hours later	127 ± 16 (5)	410 ± 38 ([illegible])	133 ± 21 (5)	139 ± 6 (5)	37 ± 54 (5)
24 hours later	118 ± 14 (6)	433 + 39* (6)	132 ± 22 (6)	121 ± 8 (6)	37 ± 100 (6)
Day 2 Isoproterenol 2nd inj					
4 hours later	76 ± 6 (5)	402 ± 29* (6)	138 ± 16 (6)	134 ± 6 (6)	43 ± 85 (6)
8 hours later	59 ± 4 (6)	4[illegible]5 ± 35 (6)	92 ± 9 (6)	148 ± 11 (6)	24 ± 30 (6)
12 hours later	50 ± 3 (6)	556 ± 31 (6)	102 ± 9 (6)	132 ± 4 (6)	24 ± 4.8 (6)
24 hours later	62 ± 5 (6)	536 ± 26* (6)	102 ± 3 (6)	121 ± 4 (6)	23 ± 16 (6)
Day 3	62 ± 8 (5)	376 ± 25 (5)	59 ± 9 (5)	123 ± 5 (5)	25 ± 08 (5)
Day 8	74 ± 12 (6)	206 ± 14 (6)	83 ± 7 (6)	135 ± 6 (6)	26 ± 10 (6)

= p < 0 001 = p < 0 05
Mean ± Standard error (n) = number of samples.

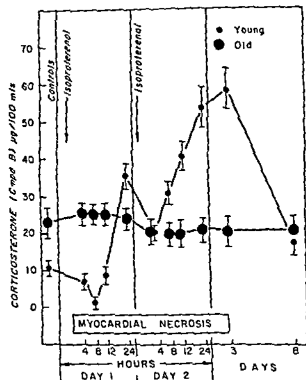


Fig 6 Changes in circulating corticosterone (Compd B)

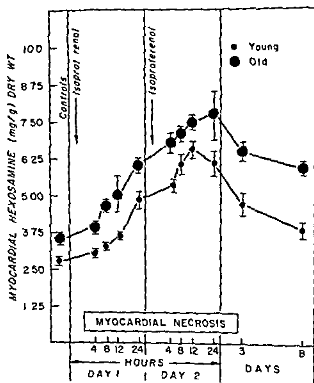


Fig 7 Changes in total myocardial hexosamine

peak on Day 3 when cardiac necrosis was most advanced receding daily but remaining well above normal until the close of the experiment (Fig 6)

Myocardial glycosaminoglycans

Total hexosamine Measurement of total hexosamine is a good index of the dynamic ground substance changes which occur in the heart during the acute stages of necrosis and repair Myocardial hexosamine levels in both the young and old rats rose in parallel reached a peak on Day 2 when myocardial necrosis was becoming established and remained elevated despite resolution of cardiac damage by Day 8 (Fig 7)

Gross and histopathologic observations On gross inspection the hearts of the old vs young rats appeared to have myocardial infarcts of equal severity i e confluent areas of myocardial necrosis involving the apex left ventricle and occasionally the right ventricle All of the animals displayed grossly visible fatty livers without any discernible differences between old and young rats In addition to the greater increase in weight the adrenal glands of the old rats were markedly more hemorrhagic than those of the young rats and concomitantly the adrenal glands of the old rats displayed much more extensive cortical lipid depletion The thymus glands of the young rats which became significantly enlarged on Day 1 were cystic and gelatinous (gross) and contained considerable colloid (histologically) There were striking differences in the myocardial histopathology between young vs old rats On Day 3 when isoproterenol induced myocardial necrosis reached a maximum the hearts of the young rats manifested extensive white blood cell infiltration and large areas of through and through necrosis (Fig 8) whereas the old rats manifested much less white blood cell infiltration but much greater interstitial edema and ground substance accumulation (Fig 9) On Days 4 through 6 when the process of myocardial repair was on going the hearts of the young rats exhibited persistent white blood cell infiltration and active fibrosis (Fig 10) whereas the hearts of the old rats manifested complete clearance of white blood cells but persistence of the myocardial edema and extra ground substance (Fig 11) By Day 8 when myocardial repair was essentially complete the hearts of the young rats showed virtually total resolution of the earlier extensive damage but persistent fibrosis which was limited to the endo

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= p < 0 001 = p < 0 05
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Fig 10 Heart of a young rat on Day 6 when myocardial repair has commenced White blood cells persist and there is intense fibroplasia (Hematoxylin and eosin original magnification ×125)



Fig 11 Myocardium of an old rat on Day 6 The intermuscular spaces persist there are few white blood cells and no active fibrosis accumulations of edema and ground substance are still present (Hematoxylin and eosin original magnification ×135)

second injection of isoproterenol (Day 2) when the process of myocardial necrosis is acutely activated Paradoxically the survival rate of the old rats improved on Day 3 when the necrosis activated 24 hours earlier by the second injection of isoproterenol reaches a zenith The explanation for this paradox may be that once necrosis is fully established the chances for arrhythmia become less Apparently acute myocardial necrosis is more lethal in old than in young rats It should be emphasized that although the area of myocardium infarcted appeared to be equal in the young and old rats the older rats received a larger total dose of isoproterenol because they were considerably heavier than their younger counterparts We[1,8] and others[14,17] have found that the cardiac stimulating effect of isoproterenol is related to body weight i e much greater myocardial necrosis is produced by isoproterenol in heavy vs light rats The half life and cardiac stimulating effect of catecholamines is prolonged by temporary sequestration in adipose tissue



Fig 8 Left ventricle of a young male Sprague Dawley rat illustrating the extensive necrosis which reaches a zenith on the third day of an isoproterenol induced myocardial infarct (Hematoxylin and eosin original magnification ×125)



Fig 9 Myocardium of an older rat showing the extensive intermuscular spaces which appear on Days 2 and 3 of a drug induced infarct These spaces are filled with edema and stain very positively for mucopolysaccharide Note the relative absence of white blood cells which are conspicuous in the younger rats (Hematoxylin and eosin original magnification ×75)

cardium (Fig 12) By direct contrast the old rats displayed no endocardial fibrosis but persistence of the intramyocardial pools of edema and extra ground substance (Fig 13)

Discussion

Our findings demonstrate that the pathophysiologic changes which attend acute myocardial infarction and repair are different in old vs young rats This is in keeping with the general clinical *experience that the pathophysiologic course of a* myocardial infarct is different in young vs old patients [11 15] Despite the dose regulated induction of myocardial infarcts of equal size (gross observation) and signs of shock and prostration of *equal severity in young and old rats* the survival rate was distinctly different Only a few young rats died but a considerable number of the old rats *succumbed* Mortality among the old rats was particularly high immediately after the



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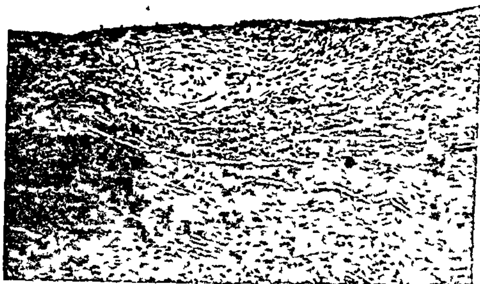


Fig 12 Heart of a young rat on Day 8 when myocardial damage is essentially resolved There is little or no evidence of the extensive earlier damage in the myocardium proper persistent and extensive fibrosis is limited to the endocardium (Hematoxylin and eosin original magnification ×125)

Therefore, although the older rats received a larger total dose of isoproterenol, our main purpose which was to maintain the area and severity of myocardium infarcted as equal as possible between young vs old rats, appears to have been achieved

Of particular interest are the specific pathophysiologic differences between the old rats and their younger brothers For example, despite the greater accumulation of ground substance and edema in the old rats, their absolute heart weight did not increase as greatly as the hearts of the young rats This difference in dynamic changes in heart weight has been a consistent observation in our comparison of the response of young vs old rats to acute myocardial infarction [8] Although the adrenal glands of the old rats were much larger than those of the younger rats and showed more intense hypertrophy hemorrhage and lipid depletion, their circulating Compound B levels were much lower than young rats This would suggest decreased steroidogenic capacity of the old rats during acute stress The initial dynamic increase in thymus size and weight in the young rats concomitant with little or no adrenal glandular hyperplasia and reduced Compound B levels followed by supernormal levels of Compound B has been our consistent experience [1,8] We believe that these pathophysiologic conditions are indicative of a temporary reduction in adrenal steroidogenesis in young rats which permits the unusual thymic hypertrophy Further we have evidence which suggests that during the early stages of myocardial ischemia, glucocorticoid steroidogenesis is impaired, consistent with the hypotensive shock At the same time, adrenal cholesterol steroid precursor material is actively being converted into mineralocorticoids, e g, aldosterone The potent sodium retaining activity of aldosterone would account for the concomitant anuria and congestive failure i e the observed hydrothorax condition The subsequent thymus gland involution, adrenal glandular enlargement, and increased glucocorticoid, e g Compound B levels concomitant with lowered aldosterone levels, would account for the restoration of blood pressure, diuresis and relief of the hydrothorax condition It would appear from the nature of the gravimetric and histopathologic changes of the adrenal and thymus glands of the old rats as well as their reduced Compound B levels that the old rats were unable to synthesize glucocorticoids as efficiently as the young rats This could account for their higher mortality rate and more profound heart failure e g, more severe and persistent hydrothorax

The use of serum enzymes as an index of acute myocardial infarction is equally as reliable in experimental as well as in clinical application Although both the young and old rats manifested a dynamic rise and fall in serum CPK SGOT SGPT and LDH levels it appeared that the young rats showed a much more vigorous increase in SGOT and SGPT levels whereas the old rats responded with more prolonged increases in CPK and LDH Because of the disparate nature of

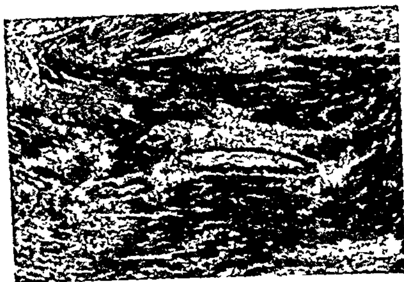


Fig 13 Heart of an old rat on Day 8 showing unresolved damage consisting of intermuscular spaces of edema and mucopolysaccharide accumulation and lack of fibroblastic repair there is no endocardial fibrosis in these old rats (cf *Fig 12*) (Hematoxylin and eosin original magnification ×125)

these serum enzyme changes it can only be suggested that the temporal nature of the myocardial necrosis must be different between young and old rats Similarly the dichotomous changes observed in circulating lipid levels between the young and old rats during acute myocardial infarction and repair also indicates a distinct difference in metabolic requirements between young vs old rats Although the young and old rats exhibited dynamic hyperlipemia initially the free fatty acid levels remained elevated in the older rats whereas total cholesterol fell to subnormal levels This rise and fall in circulating lipids is characteristic of rats subjected to an isoproterenol induced myocardial infarction [4] We believe that this dynamic lipid mobilizing effect is related to the energy requirements of the failing myocardium and is not due to isoproterenol *per se* Further this acute mobilization of lipid during the myocardial ischemia and necrosis phases is concomitant with a transient fatty liver condition That is so much lipid is metabolized by the liver at this time of acute cardiac need that there is insufficient protein to transport the excess lipid from the liver to the failing myocardium leading to temporary stasis and the fatty liver condition This fatty liver condition could also contribute to the excess circulating aldosterone and congestive heart failure which occurs at this time because of the impaired hepatic conjugation of adrenal steroids

Although the Compound B levels of the older rats were double that of the younger rats prior to the induction of myocardial infarction it is apparent that their pituitary-adrenal axis was unable to respond as effectively as the young rats to the acute stress of myocardial infarction i e very slight increase in Compound B levels in old vs a substantial increase in Compound B in young rats We[8] and others[18] have found the adrenocortical system becomes less responsive to stress with increasing age

One of the most salient features of this investigation is the distinct difference in the histopathology of the myocardium between young vs old rats Although the amount of damage in the hearts of young and old rats appeared to be equal by gross inspection histopathologic examination demonstrated a much greater and more persistent myocardial infiltration by white blood cells in the hearts of the young rats The hearts of the old rats exhibited copious and persistent edema and ground substance i e, mucopolysaccharides This latter observation is in keeping with our present finding of much greater quantities of total myocardial hexosamine in the old rats and our previous findings of accumulation of myocardial mucopolysaccharide antecedent to myocardial repair [1, 3] The marked endocardial fibrosis in the young rats vs little or no endocardial fibrosis in the old rats is remarkable and suggests that the degree of endocardial ischemia as a stimulus for fibroblastic activity was distinctly different

between young vs old rats or that ground substance metabolism and fibroplasia is funda mentally different between young and old rats

Summary

Young (90 days) and old (15 months) male, Sprague Dawley rats were subjected to an acute and massive myocardial infarct by giving them two injections of a large dose of isoproterenol The animals were autopsied at sequential time intervals to ascertain the similarities or dissimi larities in the pathophysiologic events which attend acute myocardial infarction and repair in young vs old rats Although the signs and severity of hypotensive shock appeared to be equal, mortality was higher in the old rats, especially during the acute necrosis phase The older rats also manifested more severe and persistent congestive heart failure, i e , hydrothorax Serum enzymes (CPK SGOT SGPT and LDH) lipids (triglycerides, free fatty acids and cholesterol), glucose, and BUN levels manifested a dynamic rise and fall concomitant with the induced myocardial necrosis and repair phases with distinct differences in these metabolic changes between young and old rats Despite initially higher circulating levels of corticosterone in the old vs young rats the older animals manifested little or no increase in circulating corticosterone levels during the acute stress of myocardial infarction This apparent lack of adrenocortical responsiveness was accentuated by the concomi tant finding of greatly hypertrophied, hemor rhagic and lipid depleted adrenal glands in the old rats vs a dynamic increase in circulating corticosterone levels and alterations in the weight of adrenal and thymus glands of the young rats During the myocardial repair phase, the young rats manifested extensive endocardial fibrosis whereas the old rats displayed little or no endo cardial fibrosis but copious and persistent myocardial edema and ground substance in keeping with their higher concentration of cardiac hexosamine The pathophysiologic course of events which attends myocardial necrosis and repair is quite different in young vs old rats and may be related to the degree of responsiveness of the pituitary-adrenal axis which changes with age

The author is indebted to D Conatser E Domingo W Goodhew G Williamson and J Wexler for their technical assistance and expertise

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Effects of verapamil on ventricular rhythm during acute coronary occlusion

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In the past several years verapamil has received considerable attention for use as an antiarrhythmic agent It has been shown that verapamil prevents the development of ventricular fibrillation during coronary artery ligation in dogs Zipes and associates demonstrated a slowing of the sinus node discharge rate and depression of A V conduction when verapamil was administered to dogs They also showed that verapamil lengthened the effective and functional A V nodal refractory periods Tse and Han recently reported that varapamil suppresses ouabain induced increase in automaticity in canine Purkinje fibers Verapamil was shown to prolong PR interval without affecting the QRS or QT interval in patients with ischemic heart disease Also in this report verapamil increased the degree of A V block and decreased ventricular rates in patients with atrial flutter or fibrillation More recently this drug has been shown to suppress both accelerated idioventricular rhythm and repetitive ventricular response induced by digitalis in dogs

The present study is designed to study the effects of verapamil on ventricular rhythm and some electrophysiologic parameters in the ischemic ventricle of dogs The parameters to be studied were selected as representing the mechanisms responsible for the genesis of ventricular arrhythmias during acute coronary occlusion

Methods

Experiments were performed on mongrel dogs anesthetized by an intravenous injection of sodium pentobarbital (30 to 35 mg/Kg body weight) Under artificial respiration the chest was opened in the midline and the heart was cradled in the opened pericardium A femoral artery was cannulated to record the arterial pressure and a femoral vein for administration of the drug Complete A V block and the resultant idioventricular rhythm were produced in most dogs by destroying the bundle of His with an electrical cautery knife as previously described[6] In experiments in which ventricular conduction time or fibrillation threshold was studied only the sinoatrial node was destroyed by crushing For reversible coronary occlusion the left anterior descending artery was dissecting free for a few millimeters near its origin and an occluding snare was applied around the vessel The artery was occluded about 5 minutes before each observation of specific parameters and the occlusion was released immediately following each observation Verapamil was administered intravenously in a dose of 0 2 mg/Kg body weight over a period of about 2 minutes and 5 to 10 minutes were allowed for the drug to take effect before coronary occlusion

The bipolar stimulating and recording electrodes were small steel hooks with an interelectrode distance of 2 to 3 mm A pair of stimulating electrodes was attached to the anterior septal margin of the right ventricle just outside the area

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Supported by Grant HL-18 96 from the Natio n l In titutes of H lth, and a gra t from the Americ n Heart Association N rth ast rn N w York Chapter

Received f public tio Oct 18 1977

Accepted for publ cation Dec 9 1977

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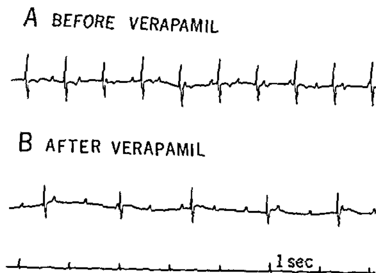


Fig 1 Effect of verapamil on idioventricular rate during acute coronary occlusion See text

of expected ischemia A pair of recording electrodes was attached to a site well within the area of expected ischemia at a distance of 50 mm from the site of stimulating electrodes Lead II electrocardiograms and local electrograms of the potentially ischemic site were recorded photographically by an Electronics for Medicine recorder at a paper speed of 100 mm per second The artifact of stimuli delivered to the stimulating electrodes was recorded on the Lead II electrocardiograms

Patterns of basic and premature stimuli were programed by using a variable interval generator The output of the interval generator triggered a Tektronix pulse generator which delivered rectangular pulses of variable duration and intensity These stimuli were also displayed on an oscilloscope and the intensity was determined by means of a Tektronix current probe amplifier The basic and premature stimuli applied through the stimulating electrodes were 2 msec in duration and twice the diastolic threshold Ventricular conduction time was measured using an oscilloscope on which sweep was triggered by the basic and premature stimuli and which displayed the stimulus artifact and the response at the recording electrodes Conduction time between the sites of stimulation and recording could be determined directly from the oscilloscope screen

Ventricular fibrillation threshold was determined by the method of Han [7] This was to apply a train of rapid square pulses across the vulnerable period following every twelfth basic ventricular response The rapid pulses were 3 msec in duration and occurred at 10 msec intervals (100 per second) The train was started at 80 to 100 msec

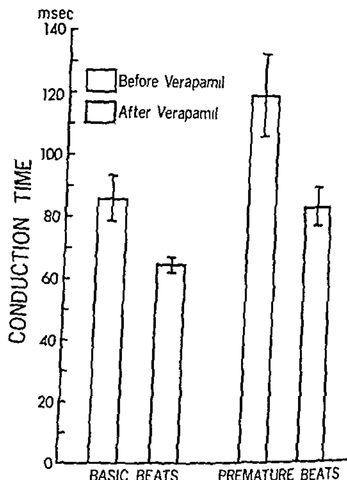


Fig 2 Effect of verapamil on ventricular conduction time of basic and premature beats during acute coronary occlusion The values are means ± S E See text

after the basic response and its duration did not extend the absolute refractory period of the first premature response evoked by the train The intensity of the rapid pulses was gradually increased until fibrillation resulted The fibrillation threshold was then defined as the minimum current in milliamps (ma) which induced fibrillation Defibrillation was immediately accomplished by DC countershock and at least 15 minutes were allowed for recovery before the subsequent test was made

Results

The effect of verapamil on idioventricular rate was studied in five dogs with complete A V block during acute coronary occlusion Fig 1 shows the results of a typical experiment in this series *Tracing A* shows an idioventricular rate of 84 beats/minute during coronary occlusion before verapamil *Tracing B* shows that the idioventricular rate is slowed to 48 beats/minute during coronary occlusion following pretreatment with verapamil The mean value of idioventricular rate

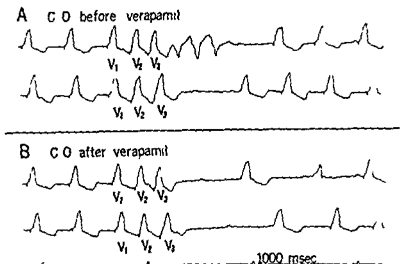


Fig 3 A and B Effects of two successive ventricular premature beats on the postextrasystolic rhythm are shown on these Lead III electrocardiograms recorded during coronary occlusion (*C O*) before verapamil (*A*) and after verapamil (*B*) *V* = the last of a series of 12 basic beats *V* = first premature beats and *V* = second premature beats See text

in the five dogs was 96 8 ± 8 6 beats/minute before verapamil and it decreased significantly to 77 6 ± 5 0 beats/minute after administration of verapamil ($P < 0\ 05$)

Six separate experiments were performed to study the effect of verapamil on ventricular conduction time during coronary occlusion Conduction time over a distance of 50 mm from the stimulating site to the recording site within the ischemic area was measured for the basic and earliest possible premature beats Fig 2 shows the results of this series of experiments The mean conduction time of basic beats during coronary occlusion was 86 0 ± 8 1 msec before verapamil and it was significantly reduced to 64 6 ± 2 8 msec after administration of the drug ($P < 0\ 03$) The mean conduction time of premature beats during coronary occlusion was 119 6 ± 13 2 msec before verapamil and it decreased significantly to 83 6 ± 6 0 msec after the drug ($P < 0\ 03$) The results indicate that verapamil is effective in improving conduction of basic and premature beats in the ischemic ventricular myocardium

Fig 3 shows the typical changes in ventricular rhythm following the introduction of two closely coupled premature beats during acute coronary occlusion In *panel A* before verapamil administration the ventricle was paced at a cycle length of 400 msec after the last of a series of 12 basic beats (V_1) the first premature beat (V_2) was introduced at the earliest possible V_1V_2 interval of 215 msec and the second premature beat (V_3) at variable V_2V_3 intervals Ventricular pacing was then interrupted for about 1 5 seconds after the premature V_2 and V_3 to observe ventricular rhythm As shown in the upper tracing three rapidly repetitive beats occurred following the premature V_3 induced at the earliest possible V_2V_3 interval of 170 msec We have concluded from our earlier studies[4,5] that these repetitive beats are most likely due to re entry resulting from depressed conduction in ischemic areas of the ventricle *In the lower tracing* the premature V_3 with a longer V_2V_3 interval of 230 msec did not produce the rapidly repetitive beats but was followed by an idioventricular escape beat with an escape interval of 805 msec

Panel B of Fig 3 depicts the same experiment as in *panel A* but after pretreatment with verapamil. *As shown in the upper tracing* rapidly repetitive beats could not be induced during coronary occlusion by the premature V_2 and V_3 of the same intervals as in *panel A* *In the lower tracing* the escape interval of idioventricular beat following the premature V_3 was lengthened to 1090 msec The results indicate that verapamil was effective in abolishing rapidly repetitive beats of the re-entrant mechanism and in increasing the escape interval of latent idioventricular pacemakers (or decreasing automaticity) during coronary occlusion

The same experiment as illustrated in Fig 3

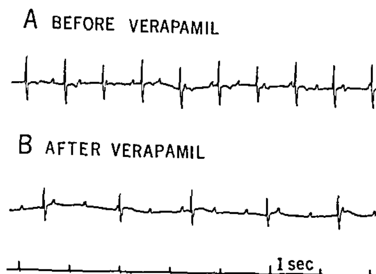


Fig 1 Effect of verapamil on idioventricular rate during acute coronary occlusion See text

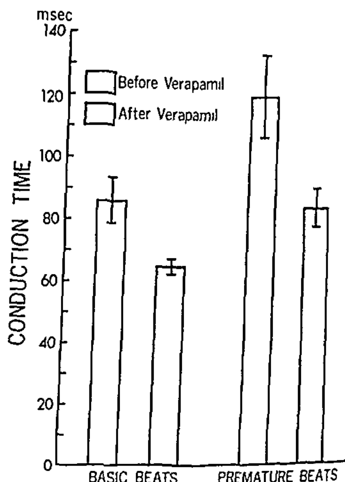


Fig 2 Effect of verapamil on ventricular conduction time of basic and premature beats during acute coronary occlusion The values are means ± S E See text

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in decreasing idioventricular automaticity under conditions of myocardial ischemia It has been previously demonstrated that idioventricular automaticity is increased during myocardial ischemia thus increasing the likelihood of ventricular arrhythmias[6] Verapamil clearly prevents this increase in automaticity and thereby reduces the probability that this mechanism could lead to cardiac arrhythmias

Another concept proposed for the genesis of ventricular arrhythmias is the mechanism of re entry [8] Because of slowed conduction or unidirectional block through the ischemic area re entrant activity may be initiated in the ischemic ventricle resulting in ventricular premature beats This may in turn set up a series of rapidly repetitive beats which degenerate into fibrillation Verapamil abolished rapidly repetitive beats in all nine of the cases in which it occurred prior to drug administration (Table I) In fact the repetitive beats and fibrillation were not observed at any time following verapamil in dogs thereby suggesting that verapamil reduces the possibility of re entrant activity The suppression of ventricular automaticity and re entrant activity by verapamil as shown in this study support the findings of Foster and colleagues[3] However the arrhythmias in our study were produced by experimental coronary artery ligation as opposed to ouabain induced arrhythmias in the study cited

One way in which verapamil may suppress the re entry mechanism is by altering myocardial conduction If conduction of an impulse through an area of ischemia was improved by a drug potential unidirectional block would be eliminated Conversely if slowed conduction was further delayed by this drug areas of bi directional block could result Both of these conditions would tend to break the re entrant pathway From the studies presented here dealing with conduction time as measured through ischemic areas verapamil improved impulse conduction in all experiments (Fig 2) These findings suggest that verapamil abolishes re-entrant activity by improving conduction through areas of potential unidirectional block and preventing the establishment of re-entrant pathways Our results show that verapamil prevented the occurrence of tachyarrhythmias during coronary occlusion in all nine cases where it had occurred during control occlusion prior to its administration Ventricular tachyarrhythmias occurring soon after coronary occlusion such as in studies of the present design are thought to be due to re entry mechanisms rather than to increased automaticity Because verapamil suppresses the re entry mechanism by improving myocardial conduction the incidence of arrhythmias was significantly reduced

Han[7] has reported that acute coronary artery ligation lowers ventricular fibrillation threshold thereby making the ventricle more vulnerable to fibrillation In the present study, verapamil significantly increased ventricular fibrillation threshold during coronary occlusion (Fig 4) This finding is also expected to decrease the likelihood of ventricular tachyarrhythmias during myocardial ischemia

The mechanism of action of verapamil as inhibitor of the slow current (or slow response) has been well documented [illegible] and the results of this study may be explained by this effect Besides slowed conduction acute myocardial infarction causes increased levels of catacholamines locally and release of potassium ions from dead and dying cells The increased levels of extracellular K could decrease the resting membrane potential of fibers in the ischemic zone and effectively prevent the normal action potential or fast response from occurring leaving only the slow response operable Due to the presence of these partially depolarized fibers increased catecholamine levels and depressed conduction, a situation now exists in which arrhythmias can be initiated by both increased automaticity or re entry These have been referred to as slow current dependent arrhythmias[11] Our results suggest that verapamil prevents the development of these slow current dependent arrhythmias by specifically inhibiting calcium current which is the major component of the slow current channel This direct inhibition of the calcium current may account for some of our observations especially suppressed re entrant activity and decreased incidence of tachyarrhythmias However, verapamil may also affect other ion fluxes either directly or indirectly as a result of its action on calcium This perhaps may explain the improvement of myocardial conduction and the increase in ventricular fibrillation threshold that has been observed This indirect effect may also explain

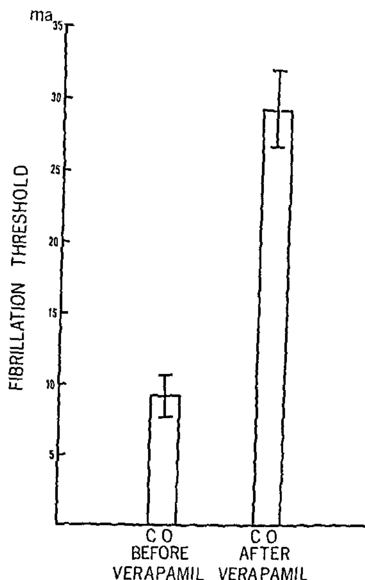


Fig 4 Comparison of ventricular fibrillation thresholds determined during acute coronary occlusion (C O) before and after verapamil administration *The values are means ± S E* See text

was carried out in 15 dogs and the results of these experiments are summarized in Table I Rapidly repetitive beats were observed in nine dogs during coronary occlusion before verapamil, and the repetitive beats degenerated into ventricular fibrillation in seven dogs Following pretreatment with verapamil, the repetitive beats and fibrilla tion were observed in none of the 15 dogs during coronary occlusion Using the idioventricular escape interval as an index of automaticity it can be seen that verapamil decreased idioventricular automaticity in 12 out of 15 dogs during acute coronary occlusion

The effect of verapamil on ventricular fibrilla tion threshold was studied in eight dogs during coronary occlusion and the results are shown in Fig 4 The mean value of fibrillation threshold during coronary occlusion was 9 3 ± 1 5 ma

Table I *Effects of* verapamil on ventricular rhythm during acute coronary occlusion (15 ex periments)

Occurrence of rapidly repetitive beats (re entry)		*Occurrence of fibrillation*		*Change in auto maticity*
Before verapamil	*After verapamil*	*Before verapamil*	*After verapamil*	*After verapamil*
9/15	0/15	7/15	0/15	Decrease 12/15 No change 3/15

before verapamil, and it increased markedly to 29 5 ± 2 8 ma after verapamil administration (P < 0 01) Our previous studies[7,8] showed that fibrillation threshold is significantly reduced in the ventricle during acute coronary occlusion The present results indicate that verapamil is effective in reversing the effect of myocardial ischemia in lowering ventricular fibrillation threshold

Discussion

Enhanced automaticity and re entry are two major mechanisms for the genesis of cardiac arrhythmias The likelihood of these events occurring in the ventricle are markedly increased during coronary artery occlusion Myocardial ischemia increases the electrophysiologic inhomo geneity of the ventricular myocardium and it is this increased inhomogeneity that most likely results in the abnormal electrical events which can lead to ventricular premature beats and fibrillation[8] This study attempts to demonstrate the effects of a new antiarrhythmic drug vera pamil on electrophysiologic parameters in the ventricle during acute myocardial ischemia In this way, the effects of this drug on important electrophysiologic parameters of myocardium such as automaticity and conduction could be determined and its efficacy as an antiarrhythmic agent can be evaluated

In the present study verapamil clearly decreased idioventricular automaticity during acute coronary occlusion Whether automaticity is measured as idioventricular rate (Fig 1) or in terms of idioventricular escape interval (Fig 3 and Table I) verapamil was consistently effective

in decreasing idioventricular automaticity under conditions of myocardial ischemia. It has been previously demonstrated that idioventricular automaticity is increased during myocardial ischemia, thus increasing the likelihood of ventricular arrhythmias.[6] Verapamil clearly prevents this increase in automaticity and thereby reduces the probability that this mechanism could lead to cardiac arrhythmias.

Another concept proposed for the genesis of ventricular arrhythmias is the mechanism of re-entry.[9] Because of slowed conduction or unidirectional block through the ischemic area, re-entrant activity may be initiated in the ischemic ventricle resulting in ventricular premature beats. This may in turn set up a series of rapidly repetitive beats which degenerate into fibrillation. Verapamil abolished rapidly repetitive beats in all nine of the cases in which it occurred prior to drug administration (Table I). In fact, the repetitive beats and fibrillation were not observed at any time following verapamil in dogs, thereby suggesting that verapamil reduces the possibility of re-entrant activity. The suppression of ventricular automaticity and re-entrant activity by verapamil as shown in this study support the findings of Foster and colleagues.[5] However, the arrhythmias in our study were produced by experimental coronary artery ligation as opposed to ouabain-induced arrhythmias in the study cited.

One way in which verapamil may suppress the re-entry mechanism is by altering myocardial conduction. If conduction of an impulse through an area of ischemia was improved by a drug, potential unidirectional block would be eliminated. Conversely, if slowed conduction was further delayed by this drug, areas of bidirectional block could result. Both of these conditions would tend to break the re-entrant pathway. From the studies presented here dealing with conduction time as measured through ischemic areas, verapamil improved impulse conduction in all experiments (Fig. 2). These findings suggest that verapamil abolishes re-entrant activity by improving conduction through areas of potential unidirectional block and preventing the establishment of re-entrant pathways. Our results show that verapamil prevented the occurrence of tachyarrhythmias during coronary occlusion in all nine cases where it had occurred during control occlusion prior to its administration. Ventricular tachyarrhythmias occurring soon after coronary occlusion, such as in studies of the present design, are thought to be due to re-entry mechanisms rather than to increased automaticity. Because verapamil suppresses the re-entry mechanism by improving myocardial conduction, the incidence of arrhythmias was significantly reduced.

Han[7] has reported that acute coronary artery ligation lowers ventricular fibrillation threshold, thereby making the ventricle more vulnerable to fibrillation. In the present study, verapamil significantly increased ventricular fibrillation threshold during coronary occlusion (Fig. 4). This finding is also expected to decrease the likelihood of ventricular tachyarrhythmias during myocardial ischemia.

The mechanism of action of verapamil as inhibitor of the slow current (or slow response) has been well documented[2,5,10] and the results of this study may be explained by this effect. Besides slowed conduction, acute myocardial infarction causes increased levels of catacholamines locally and release of potassium ions from dead and dying cells. The increased levels of extracellular K could decrease the resting membrane potential of fibers in the ischemic zone and effectively prevent the normal action potential or fast response from occurring, leaving only the slow response operable. Due to the presence of these partially depolarized fibers, increased catecholamine levels and depressed conduction, a situation now exists in which arrhythmias can be initiated by both increased automaticity or re-entry. These have been referred to as slow current dependent arrhythmias.[11] Our results suggest that verapamil prevents the development of these slow current dependent arrhythmias by specifically inhibiting calcium current which is the major component of the slow current channel. This direct inhibition of the calcium current may account for some of our observations, especially suppressed re-entrant activity and decreased incidence of tachyarrhythmias. However, verapamil may also affect other ion fluxes either directly or indirectly as a result of its action on calcium. This perhaps may explain the improvement of myocardial conduction and the increase in ventricular fibrillation threshold that has been observed. This indirect effect may also explain

the slowing of idioventricular automaticity Our preliminary microelectrode studies indeed show that verapamil decreases the slope of phase 4 spontaneous diastolic depolarization of canine Purkinje fibers

There has been a recent report[1] stating that because of its specificity for calcium verapamil may adversely effect excitation-contraction coupling resulting in hemodynamic depression However, considering our results and those of others and until such time as appropriate clinical trials are complete, verapamil must be considered as a potentially useful antiarrhythmic agent

Summary

The effects of verapamil on electrophysiologic parameters of the ventricle were studied during acute coronary occlusion in anesthetized open chest dogs Those parameters measured in the study were idioventricular automaticity, ventricular conduction, and fibrillation threshold The incidence of rapidly repetitive beats and fibrillation induced by two successive premature beats was also studied Verapamil significantly decreased idioventricular automaticity (in five dogs), improved conduction through the ischemic area (in six dogs), and increased fibrillation threshold of the ischemic ventricle (in eight dogs) The drug was effective in abolishing rapidly repetitive beats and fibrillation induced by closely coupled premature beats during acute coronary occlusion Rapidly repetitive beats occurred in nine out of 15 dogs and these repetitive beats were degenerated into fibrillation in seven dogs before verapamil Following pretreatment with the drug, rapidly repetitive beats and fibrillation occurred in none of the 15 dogs The results indicate that verapamil can be very effective against ventricular arrhythmias occurring in association with myocardial infarction

The authors wish to thank Rosalyn Grote and Susan Jones for their technical assistance and Oksana Ciupka for the preparation of this manuscript

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Case reports

Acute idiopathic pericarditis and calcific aortic stenosis unusual fatal disease combination

Charles E Wheatley M D *
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Acute idiopathic pericarditis with effusion is rarely fatal unless it complicates chronic myocardial disease Acute epimyocarditis and the impedance to ventricular filling due to pericardial tamponade further decreases the low cardiac output due to primary myocardial valvular hypertensive or atherosclerotic heart disease Treatment of acute pericarditis with effusion in the presence of chronic myocardial disease may be very difficult This presentation of a fatal case illustrates these truths

Case report

D N a 4? year-old white male Michigan National Guardman worked 36 consecutive hours on May 11 and 12 1973 despite shortness of breath to help his company prepare for weekend maneuvers He was fatigued and febrile the following day Dyspnea and cough productive of white frothy sputum developed after he walked 30 feet His oral temperature rose to 103 F during the next 5 days Dyspnea with cough at rest and a constant aching anterior chest pain which was aggravated by deep inspiration chest wall movement and the supine position appeared. Tetracycline penicillin and hydrochlorothiazide were prescribed because of basilar râles and precordial blowing systolic and apical diastolic murmurs An electrocardiogram showed left ventricular enlargement He was admitted to hospital on May 23 19 3

An illness from which he recalled no symptoms forced his absence from school for 1 year at age 1? Inactiv rheumatic heart disease with mitral stenosis was diagnosed at age 32 after a systolic murmur with a diastolic rumble was heard and cardiac fluoroscopy showed cardiac calcification An electrocardiogram was normal at that time but tracings in 19 1 showed left ventricular enlargement In 19 ? snow shoveling caused chest fullness which disappeared with rest Caugh palpitations mild shortness of breath and fever appeared in February 1973 but remitted after 3 days of bedrest Dizziness or syncope never occurred although he intermittently performed strenuous work

Admission physical examination showed a chronically ill pale mildly diaphoretic and moderately dyspneic white male with temporal muscle wasting who was unable to recline below 60 degrees due to aggravation of his chest pain and dyspnea The blood pressur was 105/50-45 both arms sitting temperature 99 8 F (oral) heart rate 90/minute respiratory rate 22/minute Neck venous distention at 60 degrees was minimal venous waves paradoxical pulse and Kussmaul s sign were absent in all positions Bilateral harsh carotid and subclavian transmitted systolic murmurs were present Carotid upstrokes were delayed but equal Eye ear nose and throat examinations were normal There were fine wet râles over the left lateral chest and bilateral basilar decreased vocal fremitus

The left border of cardiac dullness was 15 cm beyond the midsternal line 2 cm beyond the midclavicular line and the point of maximum impulse was diffuse in the sixth intercostal space The heart sounds could not be heard at the base and were greatly reduced along the left sternal border and at the apex. Extra sounds were not heard A regular rhythm at 68 beats per minute was present with occasional premature beats A harsh crescendo–decrescendo systolic murmur at the base became more high pitched along the lower left sternal border and radiated to the apex infraclavicular and interscapular areas A high pitched early and mid-diastolic decrescendo murmur was present along the left sternal border A pericardial knock and continuous friction rub were heard at the third and fourth intercostal spaces left sternal border and at the apex A slightly tender liver with a total height of 14 cm was palpable 3 cm below the right costal margin but the spleen and kidneys were not palpable Abdominal masses, bruits, and tenderness were absent The dorsalis pedis pulses were diminished but the other peripheral pulses were bounding and equal. Peripheral edema cyanosis clubbing and skin or nail changes to suggest bacterial endocarditis were absent

Elevation of leukocyte counts from 11 000 to 23 000/mm with left shift and toxic granulation suggested infection but repeat cultures of urine stool, and blood for bacteria (including M tuberculosis) fungi, yeasts, and viral agents were

Fr m the Un vers ty of Michig Medic l Cent r An Arbo Mich.
Received f r pul lication M y 20 1977
Accepted f r publ at J ly 28 1977
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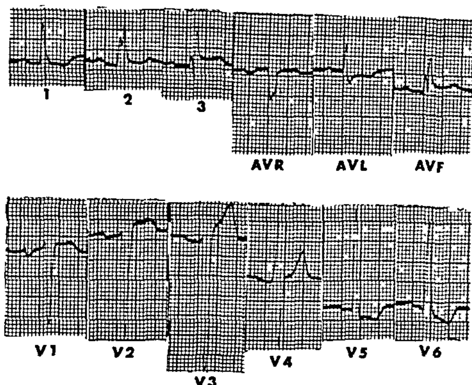


Fig 1 ECG before pericardiectomy

negative Sputum cultures grew *Candida albicans* and *Klebsiella* species Hemoglobin 11 gm per cent plasma hemoglobin 3 6 mg per cent serum iron 37 μg per cent total iron binding capacity 330 μg per cent serum haptoglobin less than 20 units suggested hemolysis and iron deficiency Screening tests for thyroid and renal disease lupus erythematosus and rheumatoid arthritis were negative Immunoglobulin electrophoresis showed elevated IgA Abnormal enzyme values were serum amylase 135 units glutamic oxalacetic transaminase 147 to 202 units glutamic pyruvic transaminase 246 units lactic dehydrogenase 318 units with increased fast fractions 1 2 Serum total bilirubin was 2 8 mg per cent Electrocardiograms showed left atrial depolarization abnormality first degree atrioventricular block left ventricular enlargement and ST elevation suggestive of pericarditis (Fig 1) Admission chest x ray showed massive water bottle enlargement of the cardiac silhouette typical of pericardial effusion and mild venous congestive changes (Fig 2)

Right heart catheterization findings (Table I) showed greater elevation of pulmonary artery diastolic pressure than severely elevated right atrial and ventricular diastolic pressures which suggested that left ventricular failure was a major cause of the low cardiac output After CO_2 and dye contrast right atrial angiocardiograms demonstrated a large pericardial effusion (Fig 3) pericardiocentesis yielded a serosanguineous fluid The patient remained very weak anoretic and tachypneic despite this procedure and an 8 lb diuresis induced by digitalis and diuretics. Pericardiectomy with removal of a large sanguineous effusion was performed

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Due to intractable congestive heart failure the patient was transferred to the University of Michigan Hospital on July 2 1973 for possible aortic valve replacement Admission physical examination confirmed previous findings and revealed an erythematous area over the hard palate and several vesicular lesions on the left buccal mucosa Urinary output and orthopnea improved after hyperalimentation which was discontinued after central venous pressure reached 22 cm H_2O He was treated for suspected septicemia with penicillin G 10 million units daily and streptomycin 1 0 Gm daily Thirteen days after admission the diastolic blood pressure dropped to 30 mm Hg and short episodes of substernal pressure like chest pain occurred

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Tissue findings

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Fig 2 Admission chest x ray before pericardiectomy



Fig 3 CO right atrial angiocardiogram Large pericardial effusion separates CO in right atrium and right heart border

and necrosis of myocardium and absence of inflammatory interstitial infiltrate Pulmonary edema and pulmonary arterial embolus Chronic passive congestion of liver with centrilobular necrosis and fatty infiltration Granulomatous mediastinal lymphadenopathy

Discussion

Acute idiopathic pericarditis is usually benign although frequently recurrent This is not true if other chronic myocardial disease is present Liu and Garcia's review[1] of the literature to 1965 reported 12 fatal cases of acute idiopathic pericarditis. Cardiac tamponade was thought to be the cause of death in five but severe chronic myocardial disease was present in six others Aortic *stenosis with myocardial hypertrophy* was present in one of these six cases An additional fatal case of idiopathic pericarditis complicating calcareous aortic stenosis and cardiac hypertrophy was reported by Kirschner and associates[2] in 1971 Their patient also had acute subendocardial (zonal) infarction without extension to the outer one-half of the myocardium Search of the English literature since 1965 did not reveal additional cases of this fatal combination of diseases

Before the advent of CO and dye contrast angiography and echocardiography the diagnosis *of pericardial effusion in the presence of* other cause for the enlargement of the heart was often made at autopsy[3] When two diseases that affect myocardial function are known to be present determination of the degree that each disease contributes to the low cardiac output may be extremely difficult[3,4] The contribution that acute epimyocarditis makes to myocardial dysfunction is speculative although myocardial biopsy may have demonstrated myocarditis Pericardial effusion with or without tamponade may mask the changes on physical examination that

Table I Catheterization findings

Site	*Before pericardiectomy pressure (mm Hg)*	*After pericardiectomy pressure (mm. Hg)*
1 Right atrium	40/30 Mean = 35	Mean = 18
2 Right ventricle	100/20 RVED = 30	85/0 RVED = 20
3 Main pulmonary artery	110/65 Mean = 75	100/30 Mean = 45
4 Left pulmonary artery wedge	–	25
5 Brachial artery	–	150/40
6 Ascending aorta	–	85 40
7 Left ventricle	–	150/10 LVED = 28

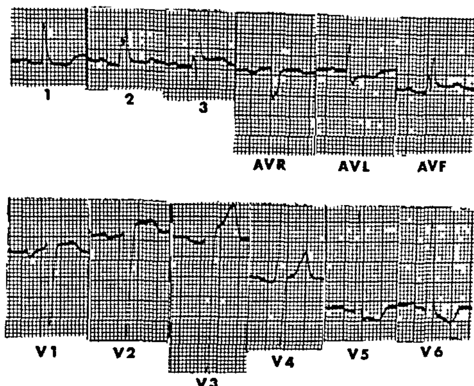


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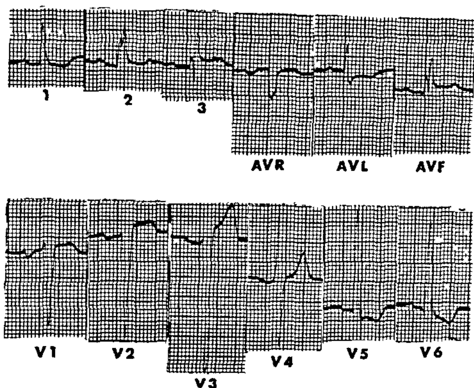


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Summary

Acute idiopathic pericarditis with massive peri cardial effusion complicated left ventricular enlargement due to calcific aortic stenosis and led to intractable congestive heart failure and death during aortic valve replacement in a 42 year old white male This unusual combination of acute and chronic diseases is lethal due to their combined deleterious effect upon myocardial function

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Fig 4 Visceral pericardium *(top right)* and epicardium with fibrinous epicarditis and myocarditis



Fig 5 Gross specimen left and right ventricular enlargement

indicate antecedent ventricular failure Pulsus paradoxus may not be produced by tamponade in the presence of aortic stenosis due to the failure of transmission of respiratory variations in left ventricular systolic pressure to the arterial system [5, 6] X ray findings of clear lung fields and a massively enlarged cardiac silhouette (Fig 1) suggest tamponade but changes on physical examination that indicate ventricular enlargement point more accurately to the cause of the greatest hemodynamic abnormality Pericardiectomy removes a lax effusion, but unless tamponade is present more severe congestive failure may follow Lange and colleagues[6] found that abnormal hemodynamic changes in nine patients with lax effusion did not improve after pericardiectomy in contrast to improvement in similar parameters in nine patients with tamponade Berglund and associates[7] state that the left ventricle stressed from outflow obstruction as in aortic stenosis dilates and produces increased pericardial pressure which limits right ventricular dia

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Isolated dissecting aneurysm of the renal artery

Asad A Bakir, M D
Suresh K Patel, M D
Melvin M Schwartz, M D
Edmund J Lewis, M D
Chicago Ill

Isolated dissecting aneurysm of the renal artery is a rare entity that gives rise to severe loin pain and hypertension, and is associated with a high incidence of vascular occlusion and renal infarction It is not clear if the disease occurs primarily or if it is an unusual complication of fibromuscular dysplasia Most reported cases have been in middle aged males This report is a presentation of two new cases and a review of the pathology, treatment, and prognosis

Case reports

Case A A 44 year old Caucasian man was admitted with bilateral dull flank pain and retro orbital and occipital headache He had been well until six months before admission when he developed severe left flank pain which radiated into the left groin There was no hematuria His blood pressure was 180/100 A urinalysis and an IVP were reported to be normal Three months before admission he had severe right flank pain radiating into the right groin Two months before admission he was started on chlorothiazide to control hypertension which had not been present in the past

The blood pressure was 150/106 There was marked fundal arteriolar narrowing but no cardiomegaly costovertebral tenderness or abdominal bruits Peripheral arm and leg pulses were present strong and of equal volume bilaterally The urine had a trace of protein with no significant sediment BUN serum creatinine and electrolytes were normal Twenty four hour creatinine clearance was 49 ml /minute Renin levels were 1 4 ng /ml /hr from the inferior vena cava 2 1 from the right renal vein and 7 1 from the left renal vein

Radiography (See Figs 1 and 2)

Surgical procedure There was no gross evidence of atherosclerosis of the aorta or the renal arteries Immediately distal to the aneurysm ofthe left renal artery the anterior division of the artery was completely occluded Within the kidney this segment gave rise to two branches that had maintained their patency by collateral flow (Fig 1) The left main renal artery the aneurysm at its bifurcation and the occluded anterior division were all excised and a Dacron tube graft was placed



Fig 1 Case A Selective left renal arteriogram The right kidney was 14 5 cm in diameter Dissecting aneurysm *(small arrow)* of the anterior division of the left renal artery Distally the anterior division is occluded *(small black arrow head)* while the posterior division *(large arrow)* is patent There is a cyst in the upper part of the left kidney *(large black arrow head)* and there are bite deformities along its lateral margin *(open arrow heads)*

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Received for publication June 28 1977

Accepted for publication July 18 1977

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Fig 2 Case A Selective right renal arteriogram The right kidney was 12 cm. in diameter Dissecting aneurysm *(large arrow)* of the anterior division of the right renal artery is noted The thin *translucent line (small arrows)* indicates dissection A posterior and an inferior division were patent. Note the string of beads appearance along the anterior branch



Fig 3 Case B Selective right inferior renal arteriogram There is absence of the nephrographic phase over the upper part of the right kidney and a prominent testicular artery *(arrow)* is seen arising from the right inferior renal artery and supplying retrograde flow to the upper part of the right kidney

Histopathology The surgical specimens showed marked fibrous intimal thickening and disruption of the internal and external elastic lamina with aneurysm formation There were areas of hemorrhage in the outer media and the inner adventitia Areas involved by the dissecting hemorrhage showed disorganization and fragmentation of the smooth muscle bundles with interposition of a homogeneous material staining Alcian blue positive

Subsequent course The patient presented a month later with a severe right flank pain Surgery was performed on the aneurysm of the right renal artery (Fig 2) Dissection was noted to have proceeded into the renal hilum and had separated the intima from the remainder of the arterial wall This artery was excised at a point proximal to the aneurysm and replaced with a Dacron tube graft.

The patient was discharged on chlorothiazide for control of mild hypertension. Two months after his second surgical procedure he was readmitted complaining of severe epigastric and right lumbar pain. A right renal arteriogram showed narrowing at the anastomotic site between the right renal artery and the patent graft The kidney size was diminished, presumably due to ischemic atrophy Renin levels by radioimmunoassay were 0.9 ng /ml./hr from the right renal vein 0 9 from the left renal vein and 0 5 from the inferior vena cava Blood pressure on diuretic therapy has since ranged between 130 to 106 systolic and 94 to 106 diastolic and the BUN has been normal.

Case B A 50-year-old Caucasian man was admitted for evaluation of renovascular hypertension Seventeen years earlier he had been told that he had "hypertension" and received therapy intermittently

Two months before admission his blood pressure was found to be 200/170 An IVP was normal except for a ring of calcification in the vicinity of the right kidney A month later renal angiography showed a significantly diminished size of the right kidney as compared to the previous IVP a loss of the nephrographic phase in the upper half of the right kidney and a bite deformity of the lateral border of the left kidney (Fig. 3)

On admission there was no loin pain or hematuria The blood pressure was 190/130 There was mild fundal arteriolar narrowing a fourth heart sound at the apex and a Grade I/IV systolic ejection murmur at the left lower sternal border There was no cardiomegaly costovertebral tenderness or abdominal bruits Peripheral arm and leg pulses were normal. The urine was unremarkable The BUN was 27 mg /dl serum creatinine 1.5 mg /dl. and creatinine clearance 81 ml /minute



Fig 4 Case B Selective left superior renal arteriogram An aneurysm is seen with a thin radiolucent line *(arrow)* suggestive of dissection One of the branches of the artery distal to the aneurysm is completely occluded *(black arrowhead)* *There is a diminution of the nephrographic phase in the shape* of a bite deformity over the lateral border of the kidney *(open arrowheads)*



Fig 5 Section of the resected left superior renal artery from Case B The *internal elastic membrane is disrupted at the site* of the dissection *(asterisk)* In this region the damaged media and intima have formed a reactive proliferating mass of spindle cells A small hematoma left from the original dissection is seen pushing against the external elastic membrane *(arrow)* (Elastic Von Giessen stain original magnification 20×)

Renin levels were 3 8 ng /ml /hr from the aorta 4 3 from the inferior vena cava 8 6 from the right superior renal vein and 3 5 from the left superior renal vein An autotransplantation was performed The left kidney was placed in the left groin
Radiography (See Figs 3 and 4)
Histopathology (See Fig 5)
Subsequent course Postoperatively hypertension persisted and proved difficult to control Three months later he was admitted with a blood pressure of 190/130 Angiography failed to show new dissection or infarcts. Renin levels were 3 1 ng / *ml /hr from the inferior vena cava 7 3 from the right superior* renal vein and 2 5 from the left renal vein Ten months later arteriography showed ischemic atrophy of the lower half of the autotransplanted kidney The BUN was 40 mg /dl the serum creatinine 2 9 mg /dl and the creatinine clearance was 26 ml /minute The *blood pressure was controlled but* labile

Discussion

Clinical features (Table I) In addition to the two patients reported here detailed observations of this phenomenon have been described in 16 cases [1-9] The mean age of the 18 patients is 52 years Fourteen of the 18 cases were males Six patients were Caucasian as well as our own two patients, race was not mentioned in the remaining ten Loin pain occurred in 11 out of the 18 patients, and was severe in eight Hypertension was present in 14 cases, while prior history of hypertension was recorded in only two cases Abdominal bruits were not found in four cases where they were sought *Microscopic hematuria* was described in four cases Gross hematuria occurred in only two patients, one of whom had cystitis

The phenomenon occurs *predominantly in the* right renal artery This artery, alone was affected in ten reported cases and there was bilateral involvement in five others (Table I) There *appears to be a predilection for the superior* branch on the right [4] No satisfactory explanation has been offered for this right sided predominance The dissection tends to extend beyond the bifurcation of the renal arteries

Hypertension pre existed in six of the 18 cases Conversely, hypertension is a common consequence *once dissection has occurred* (Table I) Atherosclerosis was absent in nine out of 13 reports and in three cases [4] it was mild involving only the aorta [4] Trauma was described in two out of the 18 cases

The major consequence of dissecting renal aneurysms is vascular occlusion with subsequent *infarction* This occurred in 12 out of the 18

Table I Characteristics of sixteen cases of isolated dissecting aneurysms of the renal arteries

Series	Age	Sex	*Past history of hypertension*	*Loin pain*	*Gross hematuria*	*Bruit*	*B P*	*Renal artery(s) involved*	*Infarction*	*Intimal rent*	*Atherosclerosis*
1 Watson, 1956											
A	52	M	–					Right	–		–
B	49	F		+ +				Both	+	–	–
2 Liebow & Cline 1956	57	M	+	+ +	+		200/150	Both	+	+	+ +
3 Gilfillan & Smart 1956	47	M	–	+ +			19?/120	Left	+	+	+
4 Henry & Burke 1963											
A	66	F	–		–		230/80	Right	+	–	Mild
B	72	M	–				120/80	Right	+	–	Mild
C	80	F	–				180/90	Right		–	Mild
5 England 1965	49	M	–	+	–		210/130	Right	+	+	+ +
6 Rosenblum 1965	55	M						Right	+	–	
7 Kincaid Smith et al 1970											
A	47	M	(–) ? mo	+ +	–		?00/125	Right	+		–
B	43	M	(–) 8 yr	+	–		180/130	Right	+		–
C	44	M	(–) 3 yr	+ +	+		20?/13?	Left	+		–
D	39	M	(–) 3 yr	+ +	–		260/180	Left			
E	4?	F	–	+ +	–		210/130	Both			
8 Perry 1971	37	M			–	–	180/120	Right	–		–
9 Kaufman et al 1973	57	M				–	?/130	Right	–		–
Current Series, 19?											
A	44	M	(+) 6 mo	+ +	–	–	150/110	Both	+	+	–
B	50	M	+		–	–	19? /134	Both	+	+	–

Pri[illegible] to admission. Abbreviations and symbols M = male F = female + = present + + = severe – = absent.

patients This complication is considered rare in classic fibromuscular dysplasia Rupture of the renal artery did not occur in any of the reported cases

Radiographic features Many typical radiographic features of this phenomenon are demonstrated in Figs 1 to 4 A characteristic feature of dissecting aneurysms is a thin radiolucent line that indicates partial separation of the intima brought about by the dissection This line was seen in both of our cases (Figs 2 to 4) Loss of the nephrographic phase and peripheral bite deformities indicate renal infarction Collateral vessels often with retrograde flow are frequently seen supplying ischemic parts of the kidney (Fig 3)

Pathology (Table I) The histopathology of the involved renal arteries in our two cases showed marked intimal fibrous thickening intimal tears medial degeneration with dissecting hemorrhage in the outer media and disruption of both the internal and external elastic lamina

Similar medial changes have been described in most of the reported cases[1-4, 8, 9] The dissecting hemorrhage occurred in the outer media or between the media and the adventitia in nine cases (Table I 1 3 5-7B 9) in addition to our own two cases Renal arterial dissections in general for example those secondary to trauma also occur along this plane of least resistance[5]

The histological changes in the renal arteries are similar to those found in fibromuscular dysplasia It has therefore been suggested[12] that a dissecting renal aneurysm forms when there is a disruptive involvement of the internal elastic lamina by fibromuscular dysplasia If this is true then dissecting aneurysms are a very uncommon complication of fibromuscular dysplasia[3, 8] The few cases of dissecting aneurysms that have been described in fibromuscular dysplasia have also shown a predilection for males This sexual bias contrasts with the experience in classic fibromuscular dysplasia a disease that affects females three times as often as males Alternatively isolated dissecting aneurysm may be a primary pathologic event leading to secondary changes in the vessel wall similar to those described in fibromuscular dysplasia[13]

Treatment and prognosis In 40 per cent of the

Table II Treatment modalities in ten patients with isolated dissecting aneurysm of the renal artery

Patient	Treatment	Follow up (mo)	B P
3	Nephrectomy†	48	C
7A	*Nephrectomy**	12	C
7B	Nephrectomy	12	C
7C	Antihypertensive medication	36	C
7D	Antihypertensive medication	10	C
7E	Antihypertensive medication	4	C
8	Nephrectomy	?	C
9	Tube Graft	12	C
Current series			
A	Tube Graft*	16	C
B	Autotransplant*	18	C

†Not known whether or not followed by antihypertensive agents
Followed by antihypertensive medication
C = *Controlled*

reported cases, renal arterial dissection was an incidental autopsy finding and had not been suspected prior to the patient s demise [1 4]

In patients diagnosed during life, various management approaches have been taken, including nephrectomy, vascular surgery and antihypertensive medication (Table II) Duration of follow-up has varied in these reports and therapeutic effectiveness has been variable Frequently, antihypertensive therapy is needed after surgical intervention The decision to undertake nephrectomy must be made in the light of the experience that the disease is bilateral in a third of the cases While the postoperative course in two out of three cases of renal revascularization was unsatisfactory, surgery for impending vascular occlusion may be appropriate Medical management alone has been effective in controlling hypertension in some patients (Table II)

Summary

We report two cases of an unusual cause of the acute onset of hypertension a spontaneous dissecting aneurysm localized to the renal artery Also reviewed are 16 reported cases from the literature The mean age of the 18 patients was 52 years The majority of these patients were males (78 per cent) Hypertension was a presenting sign in 14 (78 per cent) but was not usually a preexisting feature Loin pain often severe occurred in eleven patients (61 per cent), whereas gross hematuria was recorded only in two (11 per cent) The right renal artery was involved in ten cases (55 per cent), the left in three (17 per cent), and both in five cases (28 per cent) Atherosclerosis of the renal arteries and the aorta was absent in 69 per cent, and mild in 23 per cent There has been no report of renal artery rupture, however, vascular occlusion occurs frequently Medical and surgical approaches to the management of this phenomenon have been reported and are reviewed

Drs D Munson and M Weinberg of the Department of Cardiovascular Surgery Rush Presbyterian St Luke s Medical Center carried out the revascularization procedures in Case A Dr F Merkel of the Department of General Surgery Rush Presbyterian St Luke s Medical Center performed the renal autotransplantation in Case B The renin assays were done at Dr I D Rennie s laboratory at Rush Presbyterian St Luke s Medical Center Ms Helan Ivan and Ms Janet Iapichino did the secretarial work.

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The treatment of low renin ("primary") hyperaldosteronism

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In previous papers we reviewed the clinical biochemical and pathological features and the differential diagnosis[1] of low renin hyperaldosteronism (primary hyperaldosteronism) This paper describes the surgical and medical management of the condition

Primary hyperaldosteronism exists in a number of forms Most commonly it is associated with a unilateral adrenocortical adenoma [2-4] but in some cases an adrenal tumor is not found the adrenal glands then usually showing bilateral hyperplasia of the zona glomerulosa Rarely all the abnormalities are reversed by glucocorticoids [5] while low renin hyperaldosteronism has also been described associated with a malignant adrenocortical or ovarian tumor

Several forms of treatment are available These include adrenal surgery and drugs such as the mineralocorticoid antagonist spironolactone and the potassium conserving diuretic amiloride while rarely glucocorticoids such as dexamethasone are effective This paper describes our results with treatment and also reviews the experience of others Previous reports have described the responses to spironolactone [3] adrenal surgery [11] and amiloride [11] [35] in some of the patients in the present series

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Received for publication May 21 1976

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Patients and methods

All patients had a mean outpatient diastolic blood pressure of 100 mm Hg or more an elevated plasma aldosterone concentration (normal up to 18 ng /100 ml) on at least one occasion and with a concurrent plasma renin concentration below the mean of the normal range (less than 44 microunits per ml of International Standard Renin) Fuller details of these patients are given in a preceding paper [1] Blood pressure readings were obtained in the outpatient department and hypotensive drugs other than those specified were not used Blood pressure and biochemical values obtained from the onset to the fourth week of treatment were excluded from the analysis as were all postoperative biochemical values in the four patients who underwent total adrenalectomy Blood pressure readings within one standard deviation of the means found in a population study [13] when matched for age and sex were defined as normal

Surgery Sixty four patients (39 females) underwent adrenal surgery A single adrenocortical adenoma was found in 48 and unilateral adrenalectomy was usually performed A tumor was not identified in 14 total adrenalectomy was undertaken in four of these sub-total adrenalectomy (all of one gland and about three quarters

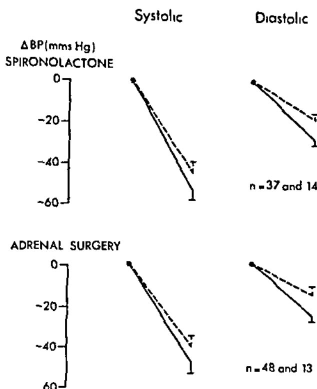


Fig 1 The mean fall in systolic and diastolic blood pressure (with S E M) in patients with *primary hyperaldosteronism* during treatment with spironolactone and after adrenal surgery *Continuous lines* represent patients with adenoma *broken lines* those in the non adenoma group All changes were statistically significant while the fall in diastolic pressure was significantly greater among adenoma patients with each treatment *(see text)*

of the other) was carried out in six while in four one adrenal gland only was removed In this group was one patient in whom a renal carcinoma was also found and nephrectomy was performed Because renal carcinoma may itself contribute to hypertension,[39] data from this patient were excluded from the following analysis The adrenal lesion in two further patients proved difficult to classify each lesion showed some histological features of an adenoma and some of a macronodule [1] There was not a significant difference in the mean duration of follow up between the groups with and without an adrenocortical adenoma (84 and 68 weeks respectively $t = 0\,64$ $0\,6 > p > 0\,5$)

Spironolactone Ninety five patients (56 females) were treated with spironolactone for a minimum period of four weeks (range 1 to 96 months mean 9 7 months) These patients received 50 to 400 mg daily (usually 300 to 400 mg daily smaller doses being used only when the hypotensive response was satisfactory) A pathological diagnosis was subsequently available in 51 patients a unilateral adrenocortical adenoma was found in 37, while in 14 a tumor was not identified the adrenal glands usually showing bilateral hyperplasia of the zona glomerulosa

Amiloride Eighteen patients (11 females) were treated with amiloride, increasing to 40 mg daily in divided doses for 6 to 8 weeks Eight of these patients subsequently underwent adrenal surgery and a unilateral adenoma was found in each A direct comparison between the effects of amiloride and spironolactone (400 mg daily) was made in each case patients were initially treated with amiloride (15 cases) or spironolactone (3 cases) and plasma levels of renin, angiotensin II and aldosterone together with total exchangeable sodium and potassium were measured on a fixed normal intake of sodium and potassium before and during each treatment Therapy was withdrawn for 6 to 8 weeks between each drug treatment Fuller details of this protocol appear elsewhere [35]

Dexamethasone Nineteen patients (9 females) in the present series received dexamethasone 0 5 mg four times daily for 14 days Nine subsequently underwent adrenal surgery and a unilateral adenoma was found in six a tumor was not identified in three the adrenal glands showing hyperplasia of the zona glomerulosa in each Blood pressure and plasma electrolytes were measured before and on the seventh and fourteenth days of treatment Plasma renin concentration was measured before and during treatment in 14, while plasma aldosterone was measured before and during treatment in 13 cases

Other methods Plasma (and serum) electrolytes blood urea plasma concentrations of renin angiotensin II and aldosterone total exchangeable sodium total exchangeable potassium total body potassium and total body water were measured as described previously [1, 3, 73] where sampling conditions are also outlined Statistical calculations were made on a Hewlett Packard 9810A calculator

Results

Adrenal surgery There was a significant fall in systolic and diastolic blood pressure after operation in both the adenoma and non adenoma groups The mean blood pressure fall after opera

Table I Comparison of variables before and after adrenal surgery (paired t test) Mean values (±S E M)

	Before treatment	*After operation*	*No of pairs*	*t*	*p*
Systolic B P (mm Hg)	204 (36)	159 (41)	63	−13 01	< 0 001
Diastolic B P (mm Hg)	1 4 (1 7)	10[illegible] (2 3)	63	−11 29	< 0 001
Plasma sodium (mEq /L)	142 8 (0 4)	139 0 (0 3)	56	−9 3[illegible]	< 0 001
Plasma potassium (mEq /L)	2 9 (0 08)	4 4 (0 06)	[illegible]	14 01	< 0 001
Plasma tCO (mEq /L)	30 1 (0 5)	24 5 (0 4)	57	−8 68	< 0 001
Blood urea (mg /100 ml)	32.3 (1 1)	46 6 (1 7)	[illegible]3	8 31	< 0 001
Plasma renin (µunits/ml)	23 2 (0 3)	63 5 (0 9)	40	.91	< 0 001
Plasma angiotensin II (pg /ml)	8 4 (1.2)	1 3 ([illegible])	11	4 06	< 0 01
Plasma aldosterone (ng /100 ml)	43 0 (4 9)	9 0 (0 8)	3[illegible]	−6 69	< 0 001
NaE (mEq)	3073 6 (106 5)	260 4 (100 1)	19	−6 5	< 0 001
NaE (mEq /kg BW)	4 2 (1 2)	39 5 (1 0)	19	−6 98	< 0 001
KE† (mEq)	2370 2 (113)	2606 4 (128 3)	18	2.53	< 0 05
KE (mEq /Kg BW)	34 6 (1 8)	38 4 (1 0)	18	2 08	0 1 > p > 0 05
Total body water (liters)	36 2	35	15	−0 99	0 4 > p > 0 3

NaE = exchangeable sodium
†KE = exchangeable potassium

tion in the adenoma group was 48/26 mm Hg and among non adenoma patients 40/15 mm Hg (Fig 1) (adenoma v non adenoma systolic t = 0 95 N S diastolic t = 2 66 p < 0 05) Blood pressure fell to the defined normal level after operation in 27 patients in the adenoma group (56 per cent) and in two patients in whom an adenoma was not found (15 per cent)

After operation (Table I) there was a significant fall in plasma sodium total exchangeable sodium and in plasma tCO_2 and aldosterone concentrations There was a significant rise in plasma and total exchangeable potassium in blood urea and in the plasma concentrations of renin and angiotensin II A small fall in total body water was not statistically significant There was a significant inverse correlation among individual patients between preoperative blood urea and the fall in blood pressure after operation (systolic r −0 35 p < 0 01 diastolic r −0 36 p < 0 01)

Spironolactone There was a highly significant fall in mean systolic and diastolic blood pressure during treatment with spironolactone (Table II) The mean blood pressure fall during treatment was 53/29 mm Hg in the adenoma group and 45/19 mm Hg among patients in whom a tumor was not found at operation (Fig 1) The fall in systolic pressure did not differ significantly between the two pathological groups (t = 1 04 0 4 > p > 0 3) but the fall in diastolic pressure was significantly greater in the adenoma group (t = 2 65 p < 0 02) (Fig 1) Blood pressure fell to normal during treatment with spironolactone in 17 patients in the adenoma group (46 per cent) and in seven patients in whom a tumor was not found (50 per cent)

No evidence of escape of blood pressure from control was seen in any patient in up to eight years of therapy Temporary withdrawal of spironolactone in patients whose blood pressure had been well controlled resulted in a rise of blood

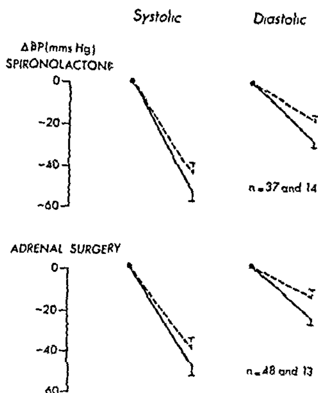


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Other methods Plasma (and serum) electrolytes blood urea, plasma concentrations of renin angiotensin II and aldosterone total exchangeable sodium total exchangeable potassium total body potassium and total body water were measured as described previously [1, 11, 15] where sampling conditions are also outlined Statistical calculations were made on a Hewlett Packard 9810A calculator

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Diastolic B P (mm. Hg)	1[illegible]4 (1[illegible])	10[illegible] ([illegible]3)	63	−11 29	< 0 001
Plasma sodium (mEq /L)	14[illegible]8 (0 4)	139 0 (0 3)	56	−9 35	< 0 001
Plasma potassium (mEq /L.)	2 9 (0 08)	4 4 (0 0[illegible])	56	14 01	< 0 001
Pla ma tCO (mEq /L.)	30 1 (0 5)	[illegible]4 5 (0 4)	53	−8 [illegible]	< 0 001
Blood urea (mg /100 mL)	3[illegible] 3 (1 1)	4[illegible] 6 (1 [illegible])	53	8 32	< 0 001
Plasma renin (μunits/ml)	23 [illegible] (0 3)	63 5 (0 9)	40	7.91	< 0 001
Plasma angiotensin II (pg /ml)	8 4 (1.2)	1[illegible] 3 (2.[illegible])	11	4 06	0 01
Plasma aldosterone (ng /100 ml)	43 0 (4 9)	9 0 (0 8)	35	−6 69	< 0 001
NaE* (mEq)	3[illegible] 3 6 (106 5)	[illegible]007 4 (100 1)	19	−6 [illegible]5	< 0 001
NaE (mEq /Kg. BW)	4[illegible] 2 (1)	39 5 (1 0)	19	−6.98	< 0 001
KE† (mEq)	23[illegible]0 2 (11 3)	[illegible]606 4 (128 3)	18	[illegible]53	< 0 05
KE (mEq /kg BW)	34 6 (1 8)	38 4 (1.0)	18	2.08	0 1 > p > 0 05
Total body water (liters)	[illegible]	35 2	15	−0 99	0 4 > p > 0 3

*NaE = exchangeable sodium
†KE = exchangeable potassium

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No evidence of escape of blood pressure from control was seen in any patient in up to eight years of therapy Temporary withdrawal of spironolactone in patients whose blood pressure had been well controlled resulted in a rise of blood

Table II Comparison of variables before and during treatment with spironolactone (paired *t* test) Mean values (±S E M)

	Before treatment	*During spironolactone*	*No of pairs*	*t*	*p*
Systolic B P (mm Hg)	198 6 (2 45)	148 1 (2 82)	95	−20 45	< 0 001
Diastolic B P (mm Hg)	121 5 (1 12)	97 3 (1 50)	95	−17 96	< 0 001
Plasma sodium (mEq /L)	142 4 (0 27)	138 2 (0 31)	83	−10 61	< 0 001
Plasma potassium (mEq /L)	3 2 (0 07)	4 6 (0 05)	85	15 91	< 0 001
Plasma tCO (mEq /L)	28 6 (0 40)	23 9 (0 33)	74	−11 2	< 0 001
Blood urea (mg /100 ml)	33 4 (1 2)	48 6 (2 1)	80	11	< 0 001
Plasma renin (μunits/ml)	26 8 (1 4)	129 5 (16 9)	45	6 12	< 0 001
Plasma angiotensin II (pg /ml)	10 2 (0 75)	57 4 (19 2)	16	2 49	< 0 05
Plasma aldosterone (ng /100 ml)	31 2 (5 0)	41 7 (5 0)	19	1 67	0 2 > p > 0 1
NaE* (mEq)	2969 4 (82 7)	2464 9 (72 7)	36	−10 55	< 0 001
NaE (mEq /Kg BW)	44 5 (1 0)	37 9 (0 9)	36	−8 18	< 0 001
KE† (mEq)	2347 0 (107 5)	2551 2 (107 1)	36	2 95	< 0 01
KE (mEq /Kg BW)	35 1 (1 4)	39 4 (1 3)	36	4 65	< 0 001
Total body water' (liters)	38 5 (1 3)	35 9 (1 4)	28	−4 73	< 0 001
Extra cellular fluid' (liters)	19 3 (0 79)	16 6 (0 82)	13	−4 31	< 0 01
Plasma volume (liters)	3 07 (0 21)	2 80 (0 24)	10	−2 27	< 0 05

NaE = exchangeable sodium
†KE = exchangeable potassium

pressure towards pretreatment levels There was an inverse correlation among individual patients between pretreatment blood urea and the fall in blood pressure during spironolactone (systolic r −0 25 p < 0 02 diastolic r −0 14 N S)

Spironolactone corrected the plasma electrolyte abnormalities in every case regardless of the hypotensive response The changes which occurred during treatment are summarised in Table II There was a significant decrease in plasma and total exchangeable sodium in total body water extracellular fluid and plasma volumes and in plasma tCO concentration There was a significant increase in plasma and total exchangeable potassium in blood urea and in plasma concentrations of renin and angiotensin II Plasma aldosterone was measured before and during treatment in 19 patients levels rose in 13 but fell in six Overall the mean change was not significant Aldosterone secretion rate was measured in two patients and values during treatment were unchanged

Changes in plasma concentrations of renin angiotensin II, and aldosterone were similar in patients with and without an adrenocortical adenoma These responses are reported in more detail elsewhere[2]

The side effects included epigastric discomfort gynecomastia Raynaud's phenomenon menstrual irregularities lassitude, cutaneous pigmentation excessive sweating and impotence However these unwanted effects were generally minor and in only three patients were they severe enough to lead to withdrawal of the drug

Table III Comparison of variables before and during treatment with amiloride (paired t test) Mean values (±S E M)

	Before treatment	During amiloride	No of pairs	t	p
Systolic B P (mm Hg)	184 (4 4)	151 (6.8)	18	−5 18	< 0 001
Diastolic (mm Hg)	114 (1 7)	101 (8)	18	−4.53	< 0 001
Plasma sodium (mEq /L)	14[illegible] 6 (0 4)	139 6 (0 5)	18	−7 0	< 0 001
Plasma potassium (mEq /L)	3 2 (0 2)	4 5 (0 1)	18	10 01	< 0 001
Plasma tCO (mEq /L)	30 1 (0 7)	[illegible]5 7 (0 5)	18	−6 43	< 0 001
Blood urea (mg /100 ml)	30 1 (1 6)	36 [illegible] ([illegible] 0)	18	4 10	< 0 001
Plasma renin (µunits/ml)	33 8 (3 3)	72 0 (13.3)	17	3 16	< 0 01
Plasma angiotensin II (pg /ml)	10 4 (1 0)	[illegible]2 5 (4.5)	16	3 09	< 0 01
Plasma aldosterone (ng /100 ml)	[illegible]5 0 (3 6)	38 5 (6 4)	16	2 49	< 0 05
NaE (mEq)	2890 (127)	25[illegible]9 (101)	17	−5 13	< 0 001
NaE (mEq /Kg BW)	4[illegible] 9 (1 1)	37 0 (0 8)	17	−5 21	< 0 001
KE† (mEq)	2[illegible]40 (159)	[illegible]840 (149)	17	3 43	< 0 01
KE (mEq /Kg BW)	37 0 (1 5)	40 9 (1.3)	1	2 5	< 0 05
Total body water (liters)	38 2 (1 9)	37 3 (1.9)	16	−0 88	0 4 > p > 0 3

NaE = exchangeable sodium
†KE = changeable potassium

Amiloride Eighteen patients were treated with amiloride and blood pressure fell in all except one There was a highly significant fall in systolic and diastolic blood pressure for the group during treatment (Table III) The mean fall in patients with a proved adenoma was 40/22 mm Hg No patient in the non adenoma group underwent adrenal surgery but quadric analysis placed five patients in this diagnostic category among these the mean fall was 18/12 mm Hg The fall in systolic pressure was significantly greater in the adenoma group ($t = 2\ 46$ $p < 0\ 05$) but the difference in diastolic response was not statistically significant ($t = 1\ 71$) Diastolic pressure fell to normal levels during amiloride in four patients with a confirmed adenoma (50 per cent) but in only one of five in the predicted non adenoma group

Other significant changes (Fig 3) included a fall in plasma and exchangeable sodium and a rise in plasma and exchangeable potassium and in blood urea while mean values of plasma renin angiotensin II and aldosterone also rose

Three patients noticed excessive flatus in the first three weeks of treatment but this symptom became less prominent as therapy continued Two complained of transient lassitude No other side effects were encountered

Comparison of adrenal surgery and spironolactone Forty four patients followed after appropriate adrenal surgery had been previously treated with spironolactone as described There was a significant correlation among individuals between the blood pressure response to each treatment (systolic $r = 0\ 66$ $p < 0\ 001$ diastolic $r = 0\ 60$ $p < 0\ 001$) The correlation was particularly close for patients in the adenoma group (systolic $r = 0\ 87$ $p < 0\ 001$ diastolic $r = 0\ 75$ $p < 0\ 001$) However data from only 10 non adenoma patients were suitable for this comparison and one patient behaved atypically in that she failed to alter her blood pressure during

Table II Comparison of variables before and during treatment with spironolactone (paired t test) Mean values (±S E M)

	Before treatment	*During spironolactone*	*No of pairs*	*t*	*p*
Systolic B P (mm Hg)	198 6 (2 45)	148 1 (2 82)	95	−20 45	< 0 001
Diastolic B P (mm Hg)	121 5 (1 12)	97 3 (1 50)	95	−17 96	< 0 001
Plasma sodium (mEq /L)	142 4 (0 27)	138 2 (0 31)	83	−10 61	< 0 001
Plasma potassium (mEq /L)	3 2 (0 07)	4 6 (0 05)	85	15 91	< 0 001
Plasma tCO_2 (mEq /L)	28 6 (0 40)	23 9 (0 33)	74	−11 2	< 0 001
Blood urea (mg /100 ml)	33 4 (1 2)	48 6 (2 1)	80	11	< 0 001
Plasma renin (μunits/ml)	26 8 (1 4)	129 5 (16 9)	45	6 12	< 0 001
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NaE* (mEq)	2969 4 (82 7)	2464 9 (72 7)	36	−10 55	< 0 001
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NaE = exchangeable sodium
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pressure towards pretreatment levels There was an inverse correlation among individual patients between pretreatment blood urea and the fall in blood pressure during spironolactone (systolic r −0 25 p < 0 02 diastolic r −0 14 N S)

Spironolactone corrected the plasma electrolyte abnormalities in every case regardless of the hypotensive response The changes which occurred during treatment are summarised in Table II There was a significant decrease in plasma and total exchangeable sodium in total body water, extracellular fluid and plasma volumes and in plasma tCO concentration There was a significant increase in plasma and total exchangeable potassium in blood urea and in plasma concentrations of renin and angiotensin II Plasma aldosterone was measured before and during treatment in 19 patients levels rose in 13 but fell in six Overall, the mean change was not significant Aldosterone secretion rate was measured in two patients and values during treatment were unchanged

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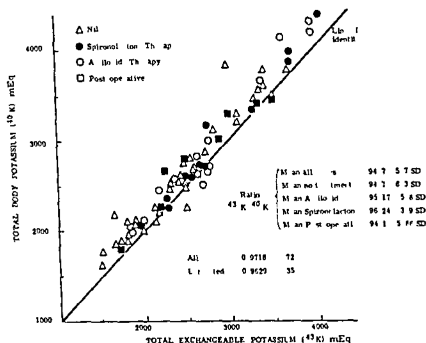


Fig 4 Relationship between concurrent estimates of total exchangeable potassium (K) and total body potassium (40K) in patients with primary hyperaldosteronism Δ = untreated ● = taking spironolactone ○ = taking amiloride ■ = postoperative

measurements of total exchangeable and total body potassium whether the patient was untreated taking amiloride or spironolactone or had been subjected to surgery thus justifying the use of exchangeable potassium as a measure of potassium status Total body potassium estimates were systematically slightly higher than exchangeable potassium estimates

Dexamethasone Blood pressure and plasma electrolytes were unchanged in all of 19 patients during dexamethasone 2 mg daily for two weeks No consistent changes in plasma renin or aldosterone concentrations were observed

Discussion

Adrenal surgery Conn and associates[1] have reviewed the literature and Conn has subsequently described his personal experience of patients following the removal of an aldosterone secreting adenoma Blood pressure was reported as normal in 60 per cent to 70 per cent and hypertension was ameliorated in most of the remainder Other reports have been in general agreement although we found that postoperative blood pressure fell to a normal level in only 50 per cent of cases[33] This expanded series is in general agreement with our earlier report

The effect of surgery on the blood pressure in non adenoma cases is less satisfactory Persistent hypertension has been reported although some fall in blood pressure may occur We have previously shown that blood pressure may occasionally fall to normal following surgery[3] but this expanded series again confirms that a smaller hypotensive response occurs in the non adenoma group

Debate continues on the choice of operative approach This may be posteriorly through the eleventh rib (bilaterally if necessary) or anteriorly through a transverse upper abdominal incision[31] The amount of adrenal tissue which should be excised from patients without tumor is also uncertain Total adrenalectomy removes the site of aldosterone production with rare exceptions but the patient is thereafter dependent on corticosteroid replacement By preserving a remnant of one gland it is hoped to avoid the need for replacement therapy while curing the aldosterone excess (corticosteroid replacement was not necessary in any of the six patients so treated in the present series) However recurrence of hyperaldosteronism after extensive adrenal surgery has been reported Less extensive adrenal surgery also leads to a smaller fall in blood pressure It is suggested that if surgery is to be worthwhile in such patients removal of one adrenal and at least three quarters of the other should be undertaken It is of interest that complete excision of

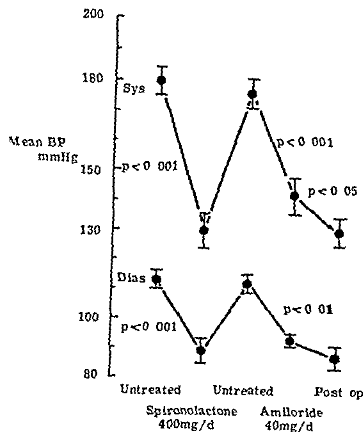


Fig 2 Mean systolic and diastolic blood pressure (± S E M) in eight patients with an aldosterone producing adenoma untreated while taking spironolactone untreated while taking amiloride and after adrenal surgery

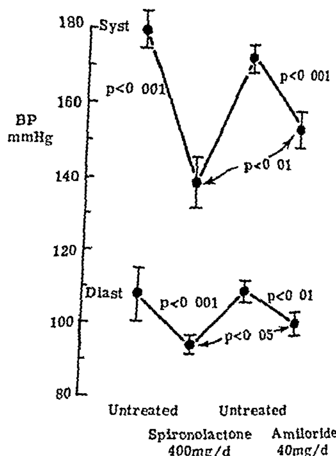


Fig 3 Mean systolic and diastolic blood pressure (± S E M) in 18 patients with primary hyperaldosteronism (both with and without adenoma) untreated while taking spironolactone untreated and while taking amiloride

spironolactone but had a considerable fall (mean 78/38 mm Hg) following total adrenalectomy [1] When this patient was excluded there was a significant correlation between the fall in diastolic pressure with the two forms of treatment (systolic r = 0 33 N S diastolic r = 0 72 p < 0 05)

The mean fall in blood pressure was again slightly greater during spironolactone treatment than after adrenal surgery both in the adenoma group (mean fall 52/27 and 46/24 mm Hg respectively) and in the group in whom an adenoma was not found (mean fall 45/20 and 36/16 mm Hg respectively) However these differences did not reach statistical significance

Both forms of treatment corrected the abnormalities of plasma electrolytes and renin concentration However the changes were slightly but consistently greater during spironolactone possibly due to a greater shrinkage in extracellular and plasma volumes with this treatment [1]

Comparison of adrenal surgery and amiloride Eight patients treated with amiloride subsequently underwent adrenal surgery and a single adenoma was found in each The hypotensive effects of amiloride spironolactone and adrenal surgery are compared in Fig 2 all three treatments produced a highly significant fall in mean systolic and diastolic blood pressure although values were slightly higher during amiloride than during spironolactone or after operation There was a positive correlation between the blood pressure response to amiloride and that following adrenal surgery although with the small numbers involved this did not reach significance (systolic r = 0 417 diastolic r = 0 673) The fall in plasma and exchangeable sodium and the rise in plasma and exchangeable potassium were not significantly different during each treatment

Comparison of spironolactone and amiloride *Both treatments produced a significant fall in systolic and diastolic blood pressures although the hypotensive effect of spironolactone was significantly greater with the doses used (Fig 3) There was a significant positive correlation among individuals between the fall in blood pressure with each form of treatment* (systolic r = 0 607 p < 0 01 diastolic r = 0 576 p < 0 02)

Relationship between total exchangeable and total body potassium As shown in Fig 4 there was a close correlation between concurrent

tion of a peptic ulcer necessitating withdrawal of the drug[41] This woman subsequently did well on amiloride Although there is little information on whether spironolactone can induce peptic ulcera tion we have previously reported a patient with no history of dyspepsia who developed a gastric ulcer during spironolactone treatment this healed rapidly following withdrawal of the drug and epigastric symptoms have not recurred[3]

Amiloride Amiloride is a pyrazine carbonyl guanidine which appears to act on sodium reab sorption in the distal renal tubule independently of aldosterone[5] When administered in five day courses amiloride was reported to correct the electrolyte abnormalities but not the hyperten sion in a patient with an aldosterone producing adenoma We have shown that prolonged treat ment in a patient unable to tolerate spironolac tone also reduced blood pressure to normal[4] The present findings confirm that amiloride can control the hypertension of primary hyperaldos teronism with or without an adrenocortical adenoma as well as correcting the electrolyte abnormalities

Comparison of surgery spironolactone and amiloride This study again confirms the close correlation between blood pressure levels during spironolactone and after adrenal sur gery [5] especially in the adenoma group Thus spironolactone is useful in predicting the blood pressure level after adrenal surgery Although numbers are still small a similar corre lation seems to be emerging between the blood pressure responses to amiloride and surgery

The fall in both systolic and diastolic pressure during spironolactone was again slightly greater than the blood pressure fall after adrenal sur gery In the doses used spironolactone was also more effective than amiloride and indeed the latter treatment was also slightly less effective than adrenal surgery We do not know whether these differences reflect the dosage of amiloride used or whether the drug is inherently less effec tive

Dexamethasone Dexamethasone was ineffec tive in correcting the abnormalities in all 19 patients studied in this series This confirms that glucocorticoid remediable hyperaldosteronism is an uncommon variant However Giebink and associates[8] have recently shown that treatment for longer than 14 days may sometimes be neces sary for aldosterone suppression in contrast to earlier cases[3,17] Probably glucocorticoid treat ment should be continued for at least four weeks when screening for this condition

Newton and Laragh administered glucocorti coids for five days to patients with primary hyperaldosteronism Aldosterone excretion fell in three rose in one and was unchanged in another Slaton and colleagues reported that dexametha sone for three days suppressed aldosterone excre tion significantly in six of fourteen patients with aldosterone producing adenoma although small er increases occurred in four others These findings are in general agreement with our own

The cause of glucocorticoid remediable hyper aldosteronism is as yet unknown A specific adre nocortical biosynthetic block has not yet been identified [6]

Adrenocortical carcinoma We have not encountered a single example of adrenocortical carcinoma producing aldosterone excess in our series of 136 patients with low renin hyperaldos teronism despite prolonged follow up in most cases and surgical exploration in 79 When recog nized or suspected prompt surgical excision is required[7]

It has been suggested that long term spirono lactone treatment in patients with primary hyperaldosteronism is unsafe because an under lying adrenal carcinoma may be overlooked [11] Crane and co workers reported a blood pressure fall to normal during spironolactone treatment in one of two such patients However these rare cases should be recognisable preoperatively[7] a large tumor may be palpable or displace the kidney on excretion pyelogram or renal arteriog raphy fever severe muscle weakness and abdom inal pain are common features and excessive secretion of adrenocorticosteroids other than aldosterone may be found[3, 9, 2, 13]

Management of the individual patient In patients with primary hyperaldosteronism asso ciated with an adrenocortical adenoma in whom preoperative spironolactone has reduced blood pressure to normal or near normal removal of the tumor bearing gland is usually the treatment of choice However when surgery is contraindicated or refused long term treatment with spironolac tone is an acceptable alternative Should the patient be unable to tolerate spironolactone amiloride may be substituted although it is

both glands has largely replaced sub total adrenalectomy in the surgical treatment of Cushing's disease [43,44]

Spironolactone Spirolactones are synthetic steroid compounds with an added lactone ring These compounds block the renal affects of aldosterone and deoxycorticosterone by competitive inhibition [45,46] In patients with primary hyperaldosteronism spirolactones cause urinary sodium excretion and potassium retention,[47,49] and when treatment is prolonged, blood pressure falls [50,5] There is also a good correlation between level of blood pressure during spironolactone treatment and after appropriate adrenal surgery [40,53,54]

Spark and Melby[40] reported a fall in blood pressure to normal in each of 20 patients with an aldosterone producing adenoma but in two further patients with low renin hyperaldosteronism and histologically normal adrenal glands, blood pressure was unaltered during treatment with spironolactone However, a satisfactory hypotensive response to spironolactone has been reported in some patients without an adrenocortical tumor [30,3,55]

This larger series confirms our previous report[3] that spironolactone produced a significant fall in blood pressure in patients both with and without adenoma However, blood pressure did not return to normal in all patients even in the adenoma group This observation was not unexpected as the removal of the cause of secondary hypertension does not always result in a fall of blood pressure to normal [56] Although the fall in systolic blood pressure did not differ significantly between the pathological groups the fall in diastolic pressure was significantly greater in the adenoma group

Plasma electrolyte abnormalities were corrected in all cases, irrespective of the blood pressure response Hyperkalemia was rare in the absence of renal impairment and resolved spontaneously when the dose of spironolactone was reduced or stopped [32] However potassium supplements were not needed and should be avoided during treatment with spironolactone The increase in blood urea during treatment may result from a decrease in glomerular filtration rate as a result of shrinkage in plasma and extracellular fluid volumes [3]

In the two patients in whom aldosterone secretion rate was measured before and during spironolactone treatment no appreciable change occurred This failure of aldosterone secretion to increase despite several simultaneous potential stimuli (increases in plasma renin, angiotensin II and potassium concentrations and in exchangeable and total body potassium with a decrease in plasma and exchangeable sodium) suggests autonomy of the adrenal adenomata in these patients Others describe a rise in aldosterone secretion[40] and excretion[50] during spironolactone, suggesting a variable degree of autonomy of such tumors Although changes in plasma aldosterone during treatment may not accurately reflect aldosterone secretion rate,[3] contrasting changes in plasma aldosterone during spironolactone might suggest variable adrenal autonomy, with spontaneous fluctuations However, the fall in plasma aldosterone levels observed in some patients might also result from a direct inhibition of aldosterone synthesis by spironolactone, an affect previously shown in the rat adrenal in vitro [57,58] Spironolactone reduced the rise in aldosterone induced by other diuretic drugs in normals [59] Such an effect was suggested by Sundsfjord and colleagues [60] who described a fall in plasma aldosterone and in aldosterone secretion in one patient with primary hyperaldosteronism treated with spironolactone In the entire present series spironolactone did not cause a significant rise in plasma aldosterone (Table II) while amiloride did (Table III) this could well reflect in part an inhibitory effect of spironolactone on aldosterone biosynthesis

By controlling hypertension and correcting electrolyte abnormalities treatment with spironolactone or amiloride should increase the safety of subsequent adrenal surgery It has also been suggested that by activating the renin angiotensin system spironolactone may reduce the risk of temporary hypoaldosteronism in the postoperative period [61] However Bravo and colleagues[4] have been unable to confirm this and suggest that spironolactone may actually contribute to post operative hypoaldosteronism by direct inhibition of aldosterone synthesis

Side effects encountered were similar to those reported previously [31,32] Contrary to the experience of others [40,61] the drug has been well tolerated in the great majority Epigastric discomfort was usually overcome by taking the drug with or after meals One patient experienced exacerba

We are grateful to G D Searle & Co High Wycombe England and to Merck Sharp & Dohme Hoddesdon England for financial support

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slightly less effective with the doses discussed The evidence suggests that when there is an unsatisfactory hypotensive response to spironolactone in adequate dosage (300 to 400 mg daily), a significantly greater fall in blood pressure after adrenal surgery is unlikely Amiloride also seems unlikely to be effective and hypertension must be controlled with other conventional hypotensive drugs However, irrespective of the effects on blood pressure, electrolyte abnormalities are invariably corrected by spironolactone, amiloride or appropriate adrenal surgery

In those patients in whom an adrenocortical tumor is not found effective adrenal surgery necessitates a total or a sub total adrenalectomy This exposes the patient to the risks of postoperative adrenal insufficiency while with more conservative surgery there is a risk of recurrence of hyperaldosteronism For these reasons the alternative of long term spironolactone is probably the treatment of choice for most such patients Should the patient be unable to tolerate spironolactone, amiloride may be substituted

Glucocorticoid remediable hyperaldosteronism responds to dexamethasone, 1 to 2 mg daily, usually within one week, although up to four weeks of treatment may be required All patients with primary hyperaldosteronism should be screened for this condition especially those in whom an adrenocortical adenoma is not identified preoperatively Dexamethasone 2 mg daily could theoretically lead to adrenal suppression when used for several weeks Others[17, 18] have administered dexamethasone 2 mg daily in divided dosage for two weeks followed by dexamethasone 1 mg daily thereafter In responsive cases blood pressure will fall and electrolyte abnormalities are corrected aldosterone values also fall while plasma concentrations of renin and angiotensin should rise Even with this regime it would seem prudent to test the adrenal responses to synthetic ACTH at the end of this period

When an adrenocortical carcinoma is diagnosed or suspected prompt surgical excision is required

Summary

Sixty four patients with low renin (primary) hyperaldosteronism underwent adrenal surgery A unilateral adrenocortical adenoma was found in 48 no tumor was identified in 14 the adrenal glands then usually showing hyperplasia of the zona glomerulosa The adrenal lesion in two further patients was difficult to classify There was a significant fall in systolic and diastolic blood pressure after operation in both the adenoma and hyperplasia groups, although the fall in diastolic pressure was significantly greater in the adenoma group Blood pressure fell to an arbitrary normal level in 56 per cent of patients with adenoma and in 15 per cent of patients in the hyperplasia group

Ninety five patients with primary hyperaldosteronism received spironolactone for a minimum period of four weeks There was a significant fall in mean systolic and diastolic pressure during treatment in both the adenoma and hyperplasia groups However, the fall in diastolic pressure was again significantly greater in the adenoma group There was a significant positive correlation between the fall in blood pressure during spironolactone and following adrenal surgery

Eighteen patients also received amiloride preoperatively and again there was a significant fall in systolic and diastolic blood pressure although levels were slightly higher than during spironolactone or after subsequent adrenal surgery Nineteen patients received a two week course of dexamethasone without effect on blood pressure or the electrolyte abnormalities

It is suggested that removal of the tumor bearing gland is usually the treatment of choice for patients with an aldosterone producing adenoma, provided preoperative spironolactone has reduced blood pressure to normal or near normal However long term spironolactone is an acceptable alternative For patients in the hyperplasia group long term spironolactone is usually the treatment of choice If this drug is not tolerated amiloride may be substituted If preoperative spironolactone does not produce a satisfactory hypotensive response adrenal surgery is unlikely to do so and hypertension should be controlled with other conventional hypotensive drugs All patients with primary hyperaldosteronism in whom an adrenocortical adenoma is not identified preoperatively should be screened for the rare glucocorticoid remediable variant Dexamethasone 1 to 2 mg daily for two to four weeks will reverse the biochemical abnormalities and reduce blood pressure When an adrenocortical carcinoma is suspected prompt surgical excision is required

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rare in developed countries *Untreated* this disorder tends to have one of four outcomes (1) progressive cardiac compression from effusion and constriction leading to death within several months (2) development of fatal tuberculosis elsewhere (3) apparent resolution with later occurrence of tuberculosis in other organs (4) apparent resolution with possible late constriction[8] Several untreated patients with bacteriologically proved tuberculous pericarditis have had delayed constriction which on histologic and bacteriologic examination showed no evidence of its tuberculous etiology[1] This discovery emphasizes the frequent difficulty in delineating the etiology of pericardial constriction but it is unlikely that tuberculosis is currently responsible for a substantial proportion of cases in the United States

The frequency of constriction with or without effusion that occurs in *treated* tuberculous pericarditis has ranged from 50 to 65 per cent[9] It may develop during therapy or years after apparent bacteriologic cure In one retrospective study four of 18 patients (22 per cent) receiving corticosteroid therapy in addition to antituberculous agents required pericardiectomy compared to five of ten patients (50 per cent) treated without corticosteroids[9] There are however no prospective controlled studies that examine whether corticosteroid therapy reduces the incidence of subsequent constriction in this or any other form of pericarditis

Fungal Patients with *disseminated* coccidioidomycosis uncommonly have pericardial involvement apparently by spread from an underlying myocardial abscess This may rarely progress to constriction One case has occurred a year following apparently uncomplicated *acute* coccidioidomycosis

Histoplasma capsulatum can cause an acute pericarditis characterized by a prodrome of fever malaise rhinorrhea and cough lasting several weeks followed by chest pain and frequently by pleural effusion The illness tends to last about ten weeks Histoplasmosis has been demonstrated by serologic changes but has not been cultured Pericardial constriction has occurred three years following acute pericarditis in one case in which organisms were demonstrated histologically but not by culture in the resected pericardium[5] Because histoplasmosis is so common in the

Table I Causes of constrictive pericarditis

Hereditary
Mulibrey nanism
Infections
Bacterial
Mycobacterial
Fungal
Viral
Parasitic
Connective tissue disorders
Rheumatoid arthritis
Systemic lupus erythematosus
Polyarteritis nodosa
Metabolic
Uremia
Trauma
Blunt or penetrating thoracic trauma
Surgery
Radiation therapy
Neoplastic
Benign or malignant pericardial tumors
Metastatic malignancy

United States this disease may be a more frequent cause of pericardial constriction than is currently recognized In addition mediastinal fibrosis an exuberant fibrosing response to histoplasma mediastinal node infection may involve the pericardium and cause constriction[16]

Viral Several viruses especially Coxsackie B[17] can apparently cause acute myopericarditis and are probably responsible for most cases of acute benign nonspecific pericarditis[1] Only rarely however has the virus actually been grown from the pericardial fluid[19] Instead a viral etiology has been inferred from serologic changes or isolation of the organism from stool or pharynx at the time of the pericarditis In some of these cases pericardial constriction has occurred several weeks to years following the acute event[20, 2] An epidemic of Coxsackie pericarditis was apparently responsible for a sudden upsurge of pericardial constriction over a three year period in Vancouver British Columbia Infectious mononucleosis an infection from Epstein Barr virus has caused a case of pericardial constriction with effusion[3]

Parasitic Perforation of an amebic liver abscess into the pericardium causes a purulent pericarditis that may rapidly constrict[1] Dracunculosis[2] rupture of an echinococcal cyst into the pericardium[26] and filariasis[7] have rarely caused pericardial constriction

Fundamentals of clinical cardiology

Pericardial constriction

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Definition and terminology

When involved by inflammation, extensive fibrosis, calcification or neoplasm, the pericardium may become rigid and impede filling of the enclosed cardiac chambers The usual term for this condition, *chronic constrictive pericarditis* is somewhat inaccurate since inflammation may be absent[1] *Pericardial constriction*, however, is especially felicitous since it suggests both constriction *of* and constriction *by* the pericardium its contraction and its compression of underlying structures The two layers are frequently fused but sometimes the constriction is mainly from the visceral pericardium (epicardium), often with a tense effusion Usually labeled *effusive-constrictive pericarditis pericardial constriction with effusion* is appropriate for this condition, where cardiac compression by *both* pericardial fluid and a rigid pericardium can cause somewhat different clinical and hemodynamic findings

Etiology (Table I)

Most cases probably originate as pericardial inflammation with exudation of fluid into the pericardial sac This is resorbed and the visceral and parietal pericardial layers then fuse Several disorders may cause the initial inflammation but in most cases no underlying etiology is evident clinically or histologically[1] Instead nonspecific fibrous tissue sometimes accompanied by calcification has replaced the original inflammatory process

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Received for publication Apr 27 1977

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Hereditary

"Mulibrey' nanism (dwarfism) found mostly in Finland, is an autosomal recessive disorder whose name is an acronym from *muscle, liver brain* and *eye* the principal organs involved Its diagnosis requires the presence of short stature plus at least two of the following four features yellow dots in the ocular fundi clinical evidence of pericardial constriction, fibrous dysplasia in the long bones, and a slightly increased basilar skull angle with a long shallow J shaped sella turcica[3] Almost all patients have had clinical evidence of pericardial constriction eight of 26 reported cases[4] have had surgical confirmation with resected tissue showing non specific fibrosis

Infections

Bacterial A wide variety of bacteria—aerobic, anaerobic and higher bacteria like Actinomyces and Nocardia—can cause purulent pericarditis by several mechanisms (1) contiguous spread from adjacent mediastinal, pulmonary or pleural infections, (2) introduction of organisms by penetrating trauma including surgery (3) contiguous spread from an underlying myocardial abscess (4) hematogenous involvement during bacteremia[5] *Acute* pericardial constriction can occur over several days to weeks in this setting cardiac compression resulting from the combination of a thickened adherent pericardium and purulent material in varying stages of organization[6] Surgical drainage is usually necessary for survival with pericardiectomy the optimal procedure[5] Rarely, *chronic* constriction may occur months to years after apparent recovery from acute purulent pericarditis if other drainage procedures were used[7]

Mycobacterial Tuberculous pericarditis is now

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the commonest underlying malignancy probably because they so often receive mediastinal irradiation and because their frequent long term survival allows the fibrosing process to develop

Neoplastic

Sometimes the neoplastic process rather than its treatment causes pericardial effusions and constriction Primary pericardial tumors both benign [2] and malignant [3] have led to constriction Malignancy of other organs most commonly breast or lung carcinoma malignant melanoma leukemia or lymphoma may cause cardiac compression by a large effusion or through neoplastic pericardial thickening

Clinical features[4, 5] (Tables II and III)

Population involved Pericardial constriction occurs in all decades of life with most series reporting an average age in the thirties Almost all have an unexplained male predominance of about 3 1 There seems to be no racial predisposition except in association with tuberculous pericarditis which has a higher incidence in blacks [55]

Symptoms The onset is typically insidious symptoms frequently being present for months to years before the diagnosis is established The most common and usually earliest complaint is exertional dyspnea a consequence of several possible mechanisms limited diaphragmatic excursion from ascites restrictive lung disease from the pleural effusions pulmonary venous hypertension In addition the arteriovenous oxygen difference increases abnormally on exercise because tachycardia cannot maintain an adequate cardiac output in the face of a stroke volume that is decreased and relatively fixed by the rigid pericardial shell Increased ventilation creating the sensation of dyspnea is necessary to ensure full oxygenation of the abnormally desaturated blood arriving in the lungs Orthopnea present in a minority of patients may be related to either the ascites or the pulmonary vascular congestion Paroxysmal nocturnal dyspnea is quite uncommon perhaps because the rigid pericardium which inhibits diastolic filling prevents the increased venous return occurring with recumbency from reaching the pulmonary vasculature Similarly frank pulmonary edema is rare

Ascites a prominent early finding often without accompanying peripheral edema results from a combination of factors The increased systemic venous pressure causes portal hypertension and impedes hepatic lymph return In addition the decreased cardiac output reduces renal perfusion, resulting in increased sodium retention The varying contribution of these factors determines whether the ascitic fluid is high in protein (from protein rich lymph) or low both circumstances having been described [56]

Peripheral edema alone or with ascites is usually present as a manifestation of the increased systemic venous pressure and sodium retention Typically most prominent in the lower extremities it may occasionally occur in the face [57]

Constitutional symptoms of weakness and fatigue are common and some patients describe weight loss and anorexia These may be the effects of hepatic congestion and a low cardiac output. Amenorrhea may occur in females

Unless the inflammatory process is still active chest discomfort is uncommon but abdominal pain in the right upper quadrant may occur from hepatic enlargement Other uncommon symptoms include dizziness or syncope and dysphagia which is probably due to left atrial impingement on the esophagus

Unusual clinical features

Localized constriction The process causing constriction usually affects the pericardium diffusely and equally Occasionally however there may be a localized area of constriction most often in patients with previous inadequate pericardiectomies but rarely without prior surgery [58] The clinical presentation has most commonly resembled infundibular pulmonary stenosis usually with right ventricular hypertrophy and failure and a calcified constricting band evident on chest roentgenogram Others have resembled mitral stenosis—from a constricting band in the atrioventricular groove[5] or pulmonary veins—and aortic stenosis—from constriction at the aortic root [59] In most of the cases these unusual features have been associated with clinical evidence of typical pericardial constriction

Protein losing enteropathy The markedly elevated systemic venous pressure may obstruct lymphatic drainage from the small intestine rarely causing substantial gastrointestinal pro

Table II Symptoms

Symptom	Approximate incidence
Dyspnea	85%
Peripheral edema	70%
Abdominal distension	65%
Weakness fatigue	30%
Orthopnea	30%
Paroxysmal nocturnal dyspnea	10%

Table III Signs

Sign	Approximate incidence[1,5]
Distended neck veins	95%
Hepatomegaly	90%
Ascites	70%
Peripheral edema	70%
Pulse pressure less than 35 mm Hg	50%
Third heart sound	40%
Pulsus paradoxus	35%
Cyanosis	25%
Splenomegaly	10%

Connective tissue disorders

Clinical and necropsy studies indicate that pericarditis, usually asymptomatic is common in rheumatoid arthritis [5] A few develop pericardial tamponade, more have pericardial constriction with at least 46 cases reported [29] There is a male predominance, and most patients have had moderate or severe arthritis for several years, usually with subcutaneous nodules and a positive rheumatoid factor The pericardial constriction has no distinctive features, although many have an accompanying pericardial effusion

Although pericarditis and effusions are frequent in systemic lupus erythematosus pericardial constriction is rare It has occurred, however, with both spontaneous[30] and drug induced[31] forms It has been associated with polyarteritis nodosa,[32] but for unknown reasons probably does not occur from the pericarditis of acute rheumatic fever [33]

Metabolic

Pericarditis occurs in the terminal stages of both acute and chronic renal failure [34] Untreated patients usually die shortly after its appearance, but it typically responds well to dialysis About 10 to 15 per cent of patients on maintenance chronic hemodialysis develop this disorder, some early in the course, but many only after months of conventional dialysis The prominent manifestations are pain and fever, the major complications tamponade and constriction The latter has occurred from six weeks to 11 months after the acute pericarditis, with an average of about six months The pathogenesis of uremic pericarditis is unknown Hemopericardium from the uremic coagulation abnormalities may be an important factor, in some cases perhaps exacerbated by systemic heparinization during hemodialysis

Trauma

The presence of blood in the pericardial sac seems to elicit inflammation which can sometimes evolve into fibrosis and pericardial constriction Whole blood injected into the pericardial sac of dogs is rapidly absorbed, leaving minimal if any, inflammation pericardial thickening and scarring When superficial myocardial or epicardial injury is inflicted with a knife and bleeding occurs, however, pericardial constriction, may develop over many months [35] These results suggest that the formation of adhesions in the pericardial cavity requires damage to the mesothelial lining This probably decreases both the mesothelial capacity to absorb blood and the normal mesothelial fibrinolytic activity Since injection of the lipid fraction of blood into the pericardial sac can produce constriction [36] the lipid components of the blood may be the most important factor in the development of inflammation and eventual constriction Alternatively, the traumatic pericardial injury may cause an immunologically mediated inflammation analagous to the post pericardiectomy syndrome [37]

One or both of these mechanisms may be involved in the constricting process sometimes observed months to years following penetrating or blunt thoracic trauma [38] Unusual etiologies include foreign bodies (needles) in the myocardium[39] and cardiac surgery, with constriction occurring several weeks postoperatively [40]

Radiation[41]

Patients receiving therapeutic mediastinal radiation may develop pericardial constriction with or without pericardial effusion several months to years later In some a preceding episode of symptomatic acute pericarditis has occurred Most have received a minimum of 4 000 rads to the heart Hodgkins s disease or other lymphomas are

Table VI Hemodynamic differentiation of pericardial constriction and cardiomyopathy

	Pericardial constriction	*Cardiomyopathy*
Left ventricular diastolic pressure–right ventricular diastolic pressure	< 6 mm Hg	> 6 mm Hg
Right ventricular diastolic pressure	$\geq 1/3$ of right ventricular systolic pressure	$< 1/3$ of right ventricular systolic pressure
Pulmonary artery systolic pressure	< 50 mm Hg	> 50 mm Hg

ascent in the jugular pulse as ventricular filling is abruptly terminated by the rigid pericardium. With normal sinus rhythm the x descent may also be prominent.[70]

The apical impulse is often inapparent because of a reduced stroke volume and the insulating and confining effect of the thickened pericardium. When the apical impulse is detectable, there may be systolic retraction. Coincident with rapid left ventricular filling, an outward thrust may occur causing an early diastolic apical impulse.[71] The heart sounds are often distant, although clear, loud sounds do not exclude the diagnosis.

A characteristic early diastolic sound, or "pericardial knock," is present in many patients. Phonocardiographic[72] and angiographic[73] studies indicate that it occurs from the abrupt halt in ventricular filling coincident with the steep upstroke of the early diastolic dip. It is best heard at the center of the precordium, is snapping in quality (often louder than S or S), and can increase in intensity on inspiration. It occurs from 0.09 to 0.13 sec following S, the shorter the interval the more severe the constriction. It therefore occurs earlier than S_3 and later than the opening snap of mitral stenosis. A pericardial friction rub is very unusual.

The chest examination may reveal dullness to percussion and decreased breath sounds from pleural thickening or effusions present in about 60 per cent. Rales from pulmonary vascular congestion are uncommon.

Hepatomegaly occurs early from hepatic engorgement and is present in nearly all patients. With prolonged disease, cardiac cirrhosis may develop and occasionally cause a decreased liver size. Splenomegaly may occur from portal hypertension.

Laboratory findings

Routine laboratory data are usually unhelpful. The hematocrit may be decreased, perhaps from the effects of chronic illness or the underlying disease. The white count is usually normal,[45] as is the sedimentation rate.[53] Urinalysis may show proteinuria varying from trace to 4+ in those with associated nephrotic syndrome. Hypoalbuminemia may be present because of hepatic dysfunction, increased urine loss with the nephrotic syndrome, or from protein losing enteropathy. Bilirubin and liver function tests may be normal or show the changes characteristic of hepatic congestion: bilirubin below 5 mg./100 ml. and often predominantly unconjugated, transaminase mildly elevated (40 to 80 u.) and rarely above 200, prothrombin time and alkaline phosphatase slightly increased.[7] Liver biopsy usually shows evidence of hepatic congestion and sometimes cardiac cirrhosis, but may be normal.[54]

Chest roentgenograph (Table IV)

Pericardial calcification, present in one half of cases, may be inapparent on posteroanterior roentgenographs but detectable on lateral or oblique projections. While pericardial calcification can occur without causing myocardial compression,[75] its presence with the clinical features of pericardial constriction is virtually diagnostic. The most frequent sites of calcification are in the coronary sulcus between the left atrium and ventricle, along the left heart border, and on the sternal or diaphragmatic surfaces of the right ventricle.[76] The presence of calcification probably reflects the duration rather than the cause of the pericardial constriction.

The cardiac silhouette may be decreased or demonstrate a diminution in size on serial films. An increased cardiac silhouette, however, is common and may occur from the pericardial thickening itself or the presence of a concomitant pericardial effusion. The left atrium may appear enlarged. There is frequently evidence of pulmonary vascular congestion and often manifestations of increased systemic venous pressure, a

Table IV Radiographic abnormalities

Abnormality	Approximate incidence
Pleural thickening or effusion	55%
Pericardial calcification	50%
Enlarged cardiac silhouette	40%

Table V Electrocardiographic abnormalities

Abnormality	Approximate incidence
Flattened or inverted T waves	95%
Low QRS voltage	65%
Notched prolonged P wave	50%
Persistent atrial fibrillation	25%

tein loss by bulk loss of lymph into the bowel lumen, often accompanied by diarrhea The hypoproteinemia that results when gastrointestinal loss exceeds hepatic production reduces the intravascular osmotic pressure and thus further encourages the formation of peripheral edema Small intestinal biopsy has demonstrated lymphangiectasia—dilated submucosal lymphatic vessels—and small bowel roentgenography may show the typical findings of that disorder mild dilatation, diffusely thickened jejunal and ileal mucosal folds, and dilution, flocculation, and segmentation of the barium column [63] There may also be gastrointestinal loss of lymphocytes (mostly T cells) in the lymph that results in impaired cell mediated immunity delayed allograft rejection, cutaneous anergy, and poor *in vitro* lymphocyte proliferative responses [64] The protein losing enteropathy, the lymphangiectasia, and the lymphocytopenia with impaired cellular immunity disappear following pericardiectomy, although sometimes only after several months

Nephrotic syndrome The nephrotic syndrome has occurred with pericardial constriction and abated weeks to months following pericardiectomy [65, 68] Renal biopsies have shown focal or diffuse membranous glomerular thickening without hypercellularity [67, 69] One case showed, in addition, diffuse tubular dilatation with focal interstitial scarring and round cell infiltration [67] The pathogenesis of this syndrome is uncertain The association of the nephrotic syndrome with renal vein thrombosis suggests that increased renal vein pressure may be responsible in both circumstances In most cases however renal vein thrombosis is a complication, not a cause, of the nephrotic syndrome [69]

Physical examination Many patients look chronically ill, the decreased muscle mass a sharp contrast to a protuberant abdomen and the prominent peripheral edema This appearance frequently suggests a serious systemic disease such as metastatic malignancy or a primary liver disorder

The patients are afebrile unless the underlying inflammatory process is still active The rhythm is atrial fibrillation in about 25 per cent and atrial flutter in about 5 per cent These arrhythmias presumably arise from the stretch and distortion of the atrial conduction system by an increased atrial pressure, but may also be due to inflammatory or fibrotic involvement of the sinoatrial node Hypertension is very uncommon, and the pulse pressue is often low (less than 35 mm Hg), reflecting the decreased stroke volume Pulsus paradoxus, an inspiratory decrease of greater than 10 mm Hg in systolic pressure, is uncommon unless there is an associated pericardial effusion, presumably because the rigid pericardial shell is relatively unaffected by changes in intrathoracic pressure

Examination of the jugular venous pulse is the single most important physical observation Unless the patient has undergone vigorous diuretic therapy, which can reduce the systemic venous pressure to normal the jugular venous pressure is virtually always elevated Frequently the veins are distended to the mandibular angle in the upright position Inspiratory distension of the cervical veins (Kussmaul s sign) indicating an increased inspiratory venous return that the encased right ventricle is unable to accept is present in a minority of patients The high venous pressure may obscure this sign as well as the pulse waves [49] When visible the jugular waves often show a rapid y descent occurring at the time of tricuspid valve opening This results from the brisk but brief inflow of blood into the right ventricle from the high right atrial pressure The presence of a rapid y descent excludes the diagnosis of tricuspid stenosis [49] which also has the clinical features of a high systemic venous pressure The rapid y descent is followed by rapid

contractility have varied (dp/dt, V_{max}), and measurements of circumferential fiber shortening have been normal[34] or decreased.[6] The differences may, in part, reflect the degree of myocardial fibrosis and atrophy present.

With exercise[91] the cardiac output is subnormal in relationship to the increased oxygen consumption. The AV O_2 difference widens abnormally. The stroke volume fails to increase because of limitations to diastolic filling. There is a marked elevation in right ventricular diastolic pressure, but the difference between left and right diastolic pressures remains low and essentially unchanged.[18]

The angiographic findings may include increased extraluminal soft tissue thickness along the lower right heart border, straightening and immobility of the right atrial border, superior vena caval dilatation, and left atrial enlargement. While coronary arteriography is not routinely indicated unless it is necessary to exclude the presence of ischemic heart disease, it does show extension of the heart shadow beyond the ventricular epicardium as delineated by the coronary arteries. This finding indicates pericardial thickening and/or fluid.[92]

Features of pericardial constriction with effusion[7, 93]

Patients having pericardial constriction with effusion tend to be somewhat younger than those with pericardial constriction alone. The most frequent causes are idiopathic (many presumably viral), radiation therapy, uremia, neoplasm, or rheumatoid arthritis. The duration of symptoms is typically weeks to months rather than years, and unlike pericardial constriction alone, there is frequently a preceding history of acute pericarditis with fever, pleuritic chest pain, and pericardial friction rub. The symptoms are similar—dyspnea, abdominal distension, and ankle edema most prominently—but some physical features differ. Paradoxical pulse is more common, but Kussmaul's sign and the diastolic knock are unusual. While there are T wave flattening and inversion and frequently low voltage, abnormal P waves and atrial fibrillation are generally absent. The cardiac silhouette is usually enlarged on chest roentgenogram, and pericardial calcification is rare. The catheterization results show a generally higher right atrial pressure that decreases to the usual level seen in pericardial constriction following pericardiocentesis. The *x* descent is predominant or equal to the *y* descent; predominant *y* descent is not seen until pericardial fluid is removed. At operation there is extensive thickening of both visceral and parietal pericardial layers, with the pericardial space generally containing several hundred c.c. of fluid, often bloody, always high in protein, and frequently tense. As with pericardial constriction alone, there may be underlying myocardial atrophy. Pericardial constriction with effusion can develop into pericardial constriction alone over a period of weeks to months and, in fact, may be a common stage in the evolution of pericardial constriction.

Complications

Myocardial fibrosis. Perhaps in part from disuse, pericardial constriction can cause myocardial fiber atrophy and fibrosis. In 11 patients dying with chronic pericardial constriction, muscle fiber thickness was uniformly reduced throughout both ventricles. The muscle atrophy seemed related to neither the duration of symptoms nor the thickness of the pericardium.[94] Some patients may have replacement of muscle fibers by fibrous tissue, at times causing electrocardiographic changes typical of a myocardial infarction in the affected area.[84] Myocardial atrophy or fibrosis may also be responsible for the refractory cardiac failure occasionally following pericardiectomy, when the myocardium appears unable to handle the increased volume load.

Cardiac cirrhosis.[95] The increased systemic venous pressure of pericardial constriction almost always causes severe hepatic congestion, which, when prolonged, can lead to cardiac cirrhosis. In this entity there is central atrophy with fibrous bridging between central vein areas. The hepatic congestion seems to cause some cellular destruction, promoting a reparative fibrogenesis in the damaged centrilobular areas. Clear differentiation from simple hepatic congestion is impossible by clinical or biochemical features alone; cardiac cirrhosis may have no associated abnormalities in liver function tests, and its presence does not seem to increase the incidence of portal hypertension, splenomegaly, ascites, or esophageal varices. Perhaps the

widened right upper mediastinum from an enlarged superior vena caval shadow and distended azygous vein[76,78] Pleural effusions, present in about 60 per cent, are usually bilateral, when unilateral, they are typically, though not uniformly, right sided Pleural thickening or scarring from the original inflammatory event may also be visible On fluoroscopy the cardiac pulsations are usually, but not always, diminished or absent

Electrocardiogram[79,82] (Table V)

The electrocardiogram is rarely normal Atrial fibrillation is present in about 25 per cent, atrial flutter in 5 per cent Paroxysmal supraventricular tachycardia and both supraventricular and ventricular extrasystoles occasionally occur The P wave is often notched and prolonged (> 0.10 sec) resembling "P mitrale," and presumably occurring from left atrial hypertension and enlargement The P R interval is usually normal The QRS complex often shows decreased voltage, at times confined to the limb leads Some patients may show abnormal Q waves characteristic of myocardial infarction These patients have myocardial fibrosis in the involved area at autopsy[80] The QRS axis is usually normal but some show right axis deviation ($>$ 100 degrees) with or without evidence of right ventricular hypertrophy ($R/S > 1$ in V_1) These features are unexplained, since ventricular hypertrophy is not a pathologic feature of the disease Left axis deviation and left ventricular hypertrophy are rare A pattern of incomplete right bundle branch block occasionally occurs

The most common findings, seen in nearly all patients are nonspecific T wave changes—low flat biphasic or inverted T waves in leads where they are normally upright In a minority there is accompanying ST segment depression These changes may represent myocardial involvement from subepicardial penetration of the primary pericardial inflammatory process myocardial atrophy and fibrosis simultaneous involvement of the myocardium and pericardium by the same pathologic process impairment of coronary flow or unrelated coronary artery disease[8]

Echocardiography usually demonstrates an unexplained paradoxical motion of the interventricular septum similar to that seen in right ventricular flow overload syndromes such as atrial septal defect[83,84] Evaluation of pericardial thickness is usually difficult and unhelpful but the echocardiogram is sensitive in detecting any fluid in those with associated pericardial effusion It may also be useful in assessing ventricular size and function

Cardiac catheterization[85] and angiography[86,87]

The most important diagnostic procedure is cardiac catheterization, best performed on both right and left sides of the heart and employing angiocardiography Since all diastolic expansion is restricted by the rigid pericardium, all diastolic pressures are elevated and approximately equal, even following exercise The difference between right and left diastolic pressures rarely exceeds 5 to 6 mm Hg Thus, the diastolic pressures in the left and right atria and ventricles and the pulmonary artery are nearly equal

The right atrial pressure usually shows no respiratory variation, but an inspiratory increase (Kussmaul s sign) may be present in some severe cases In sinus rhythm the a and V waves are approximately equal and followed by rapid x and y descents because of the high filling pressure This gives the typical M or W wave form Concurrent with the right atrial y descent is a deep diastolic dip in the right ventricular pressure as rapid filling begins This pressure quickly rises to a plateau as the rigid pericardium impedes further filling This dip and plateau pattern, resembling a square root sign is also present in left ventricular diastolic tracings

Substantial pulmonary hypertension is rare most pulmonary arterial systolic pressures being less than 45 mm Hg The pulmonary capillary wedge pressure tracing has a wave form similar to that of the right atrium Unless vigorous diuresis has caused hypovolemia the ventricular filling pressures are elevated typically to levels between 12 and 25 mm Hg depending on the severity of constriction Pulsus paradoxus occurs in a minority of patients more frequently in those with an associated pericardial effusion

In most cases[88] the cardiac index and stroke index are low normal or decreased The left ventricular end diastolic volume is reduced in all but mild cases and reflects the severity of constriction The ejection fraction is usually normal but may sometimes be substantially diminished[8] Isovolumic and ejection indices of

existence for 5 to 15 years with repeated paracentesis [1] a procedure apparently unattended by any significant or deleterious hemodynamic consequences despite the removal of large quantities of fluid [1,2] An occasional patient has survived for several decades without surgery one of Paul Dudley White s cases having had symptoms for 44 years [4] Although some patients respond to vigorous diuretic therapy the treatment of pericardial constriction is pericardiectomy whose delay may risk the development of myocardial atrophy and fibrosis The surgical mortality rate is small (5 to 10 per cent[10,5]) and the outcome excellent with about 80 to 90 per cent obtaining complete symptomatic relief Few derive no benefit

The basic requirement for surgery is a thorough decortication with the removal of both visceral and parietal pericardial layers from the right and left ventricles Resection over the left ventricle should proceed at least as far posterolaterally as the phrenic nerve [10,3] The approach has varied including median sternotomy which most surgeons favor and left thoractomy the important point is obtaining excellent exposure It is probably wise to free the left ventricle first to avoid pulmonary congestion when release of the right ventricle increases pulmonary blood flow and volume Calcification may require bone cutting instruments and in places may so invade the myocardium that removal is impossible The necessity of decorticating the atria and vena cava in the absence of obvious constricting bands is debated [9,05] this procedure increases the risk and is probably unimportant in most patients

Hemodynamic measurements immediately following pericardiectomy may show normal values in all chambers normal left atrial and ventricular values with improved but still abnormal right atrial and ventricular measurements or no immediate changes [06] Over the next few days however central venous pressure begins to fall and ordinarily reaches normal levels within four weeks The pulse pressure increases as stroke volume becomes normal Cardiac catheterization studies two to five months following surgery demonstrate satisfactory hemodynamic indices in almost all patients These findings suggest that in some patients there may be reversible myocardial impairment requiring several days to abate following pericardiectomy [7]

Electrocardiographic abnormalities often resolve postoperatively The frequently abnormal P wave usually reverts to normal low voltage increases most flat or inverted T waves become upright and right axis deviation disappears Those with the pattern of incomplete right bundle branch block have no change and atrial fibrillation typically persists [3]

A few patients have persistently abnormal hemodynamic values following surgery Probably the most common reason is incomplete pericardiectomy [10] Some patients however have substantial myocardial atrophy and fibrosis [9] They may die shortly after surgery from unremitting cardiac failure the pericardiectomy had the effect of increasing pulmonary blood flow which the left ventricle cannot effectively accept Others survive surgery but have derived little or no benefit from it Which patients will not respond to decortication is unpredictable significantly diminished left ventricular function which may persist postoperatively does not preclude improvement in symptoms or other hemodynamic measurements [6] Hence virtually all patients should receive surgical therapy with the recognition that in a very small number the results will be unimpressive or even catastrophic

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Differential diagnosis

Unexplained exertional dyspnea, ascites, peripheral edema, or pleural effusions should suggest pericardial constriction. The diagnosis is missed with striking and disconcerting regularity. Hepatic cirrhosis, metastatic malignancy, and Meig's syndrome in females are among the most frequent mistaken diagnoses. Careful examination of the jugular venous pulse, which is elevated in pericardial constriction but normal or low in these other disorders, should prevent such errors.

Most difficult to distinguish from pericardial constriction are the cardiomyopathies, particularly the restrictive forms resulting from such processes as diffuse fibrosis following myocarditis, idiopathic hypertrophy, or infiltrative diseases like *amyloidosis, hemochromatosis, or sarcoidosis*. In the absence of pericardial calcification or some *manifestation of the systemic disorder causing* the cardiomyopathy, the sometimes strikingly similar clinical and hemodynamic findings may make clinical differentiation impossible without exploratory surgery. Both cardiomyopathies and pericardial constriction may have clinical features of increased systemic and pulmonary venous pressures, the S_3 of left ventricular failure may be mistaken for a "diastolic knock," and the electrocardiographic findings may be identical. Cardiac catheterization in restrictive cardiomyopathy may also show increased systemic and pulmonary venous pressures displaying the *M* or *W* configuration and an early diastolic dip and plateau pattern of ventricular pressure.[96] While certain findings on catheterization may help to distinguish these disorders, sometimes even this procedure is inconclusive, and surgical exploration becomes necessary.

Findings favoring a cardiomyopathy are episodes of acute pulmonary edema, a prominent apical impulse displaced well to the left, an audible S_4, and electrocardiographic evidence of left ventricular hypertrophy or bundle branch block.[97] Of the hemodynamic findings (Table VI) the difference between *right and left diastolic* pressures is the most reliable point in the differential diagnosis, but even it may be misleading.[1,9] In the cardiomyopathies the diastolic pressures in both ventricles may be elevated but because the heart is not encased in a rigid shell as in pericardial constriction, they are very unlikely to be equal. *In* restrictive cardiomyopathy the reduction in diastolic compliance is greater in left than *right ventricle, giving a higher left ventric*ular diastolic pressure and a difference between the two of greater than 6 mm Hg. Exercise enhances this difference. This value is almost always less than 6 in pericardial constriction even with exercise. Other differential points include the pulmonary artery systolic pressure which is usually less than 50 mm Hg with pericardial constriction, but greater in the cardiomyopathies. In addition, left ventricular systolic function is usually normal in pericardial constriction, but abnormal in the cardiomyopathies.

Several noninvasive techniques reflect these differences. Echocardiography or radionuclide angiography showing a small left ventricular cavity with good ventricular function in a patient with predominantly right-sided failure should *suggest pericardial constriction and the need* for cardiac catheterization. Systolic time intervals will usually show a short pre-ejection period (PEP), a long left ventricular ejection time (LVET), and a low PEP/LVET ratio (less than *0.5*).[99] Simultaneous jugular venous pulse tracing and phonocardiography demonstrate that the interval from the aortic component of the second sound to the peak of the jugular venous *V* wave is usually less than 0.03 sec in pericardial constriction, greater in cardiomyopathies.[100]

These noninvasive tests are helpful but not completely reliable in differentiating the two disorders. In perplexing cases cardiac catheterization or even exploratory surgery is necessary to exclude the eminently *treatable entity of pericar*dial constriction. Noninvasive techniques may be more dangerous to the patient than invasive ones if they result in a missed or significantly delayed diagnosis.

Treatment

Since no reported large series of untreated patients exists, the natural history of pericardial constriction is uncertain. Young children seemed less capable of prolonged survival than adults, most dying within one to three years after the appearance of massive ascites. Adults could survive, albeit frequently with a valetudinarian

existence for 5 to 15 years with repeated paracentesis[101] a procedure apparently unattended by any significant or deleterious hemodynamic consequences despite the removal of large quantities of fluid[102] An occasional patient has survived for several decades without surgery one of Paul Dudley White s cases having had symptoms for 44 years[4] Although some patients respond to vigorous diuretic therapy the treatment of pericardial constriction is pericardiectomy whose delay may risk the development of myocardial atrophy and fibrosis The surgical mortality rate is small (5 to 10 per cent[9,33]) and the outcome excellent with about 80 to 90 per cent obtaining complete symptomatic relief Few derive no benefit

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Infective endocarditis New diagnostic techniques

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Recent reviews of infective endocarditis (IE) have documented changes in predisposing factors etiology and the clinical characteristics of this infection[1] Although atypical or unusual manifestations of IE are often stressed the majority of cases may be diagnosed using clinical criteria and blood culture results In the past several years new diagnostic tests have been used in assessing patients with IE While some of these tests may provide clinically useful information it is important to critically evaluate these techniques and to determine which patients would benefit from such studies Blood cultures positive in approximately 85 per cent of patients with IE continue to be the most definitive study Blood culture results will be compared in terms of sensitivity and specificity to newer diagnostic techniques

Blood cultures

Infectious endocarditis and other intravascular infections such as mycotic aneurysms and infected arteriovenous fistulas are characterized by bacteremia which is continuous In contrast positive blood cultures persist for less than 30 minutes in patients who have a low inoculum of bacteria since organisms are effectively cleared by the reticuloendothelial system[2] The rapid removal of pathogenic bacteria from the blood has also been demonstrated when larger inocula are given to experimental animals The persistent bacteremia seen with IE is due to organisms which are constantly seeded into the blood from vegetations Blood cultures in patients with endocarditis should therefore be drawn in a way that will not only document bacteremia but also indicate its persistence

The use of proper techniques in obtaining blood cultures cannot be overemphasized At least three cultures should be obtained over a period of hours to days in patients with suspected endocarditis More than six blood cultures are rarely necessary The timing of the cultures will often depend on the severity of the illness and the need for rapid institution of therapy Alternative venepuncture sites should be meticulously prepared with a 2 per cent iodine solution followed by 70 per cent alcohol to remove the iodine Arterial samples offer no advantage over antecubital vein cultures[2] Several milliliters of blood are inoculated into each of two liquid medias routine blood sets consist of an aerobic and an anaerobic bottle The amount of blood to be inoculated is specified by each manufacturer The aerobic bottle is under a partial vacuum and should be routinely aerated after blood collection Blood culture sets are generally adequate for the isolation of aerobic and anaerobic bacteria Routine subculturing and incubation for up to 21 days is necessary when cultures are negative since IE occasionally is caused by slow growing or nutritionally fastidious organisms

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Received for publication Feb 24 19 8

Reprint requests Michael H Miller M D Department of Medicine Division of Infectious Diseases Montefiore Hospital and Medical Center Bronx N Y 10467

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Infective endocarditis New diagnostic techniques

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Recent reviews of infective endocarditis (IE) have documented changes in predisposing factors etiology and the clinical characteristics of this infection Although atypical or unusual manifestations of IE are often stressed the majority of cases may be diagnosed using clinical criteria and blood culture results In the past several years new diagnostic tests have been used in assessing patients with IE While some of these tests may provide clinically useful information it is important to critically evaluate these techniques and to determine which patients would benefit from such studies Blood cultures positive in approximately 85 per cent of patients with IE continue to be the most definitive study Blood culture results will be compared in terms of sensitivity and specificity to newer diagnostic techniques

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0002 8 03/78/0196-0123$00 60/0 © 1978 The C V Mosby Co

inactivate antibiotics which may have been carried over into the culture flask from the patient's blood The addition of a beta lactamase (penicillinase) to the medium may be helpful in patients who have received penicillins or cephalosporins Care should be taken not to over inoculate the blood culture bottle Antibiotics in the blood will be diluted by the larger volume of liquid culture medium decreasing their activity The presence of cell wall deficient forms should be sought in patients who have received agents whose primary activity is on the cell wall Such drugs include the penicillins, cephalosporins, and vancomycin Since cell wall deficient forms of bacteria will not grow on ordinary media a hypertonic medium such as broth with 10 per cent sucrose should be used in addition to the routine blood culture bottles Organisms requiring special growth factors not present in standard media are sometimes seen on Gram stain from patients with IE The use of enriched medium may permit the isolation of these organisms[6] Although thioglycollate or other anaerobic blood culture media will usually support the growth of anaerobes routine subculturing and the incubation of bottles for many days are especially important when anaerobic endocarditis is suspected Patients with gastrointestinal disease or prosthetic valve endocarditis account for most cases of anaerobic IE Fungal endocarditis is another important cause of culture negative endocarditis Candida species are more often associated with positive cultures than other fungi such as histoplasma or aspergillus species The fungemia associated with candida endocarditis may not be continuous and often many days are required for the isolation of this pathogen The use of biphasic medium[7] and the aeration of bottles facilitate the isolation of these pathogens Routine aeration of one bottle may also facilitate the isolation of some bacteria such as pseudomonas species Fungal endocarditis should be suspected in the presence of drug addiction, following prosthetic valve replacement and in patients with intravenous or urinary catheters who have received parenteral antibiotic therapy The presence of large emboli in culture negative IE also suggest a fungal etiology and the histologic and bacteriologic examination of material removed at embolectomy may provide a diagnosis

The examination of peripheral leukocytes for the presence of bacteria may be useful in some patients with IE[9] False negative results, however, are not uncommon,[10] and the differentiation of bacteria from artifacts may be difficult

Echocardiography

Echocardiography has been used in assessing patients with IE Vegetations have been documented on the aortic, mitral, and tricuspid valves The sensitivity of this procedure is related to the size of the vegetation

In some clinical settings, echocardiography is a useful diagnostic procedure Patients with aortic insufficiency of unknown etiology may be diagnosed as having IE by the demonstration of vegetations on the aortic valves[11] This technique may also be useful in patients with culture negative fungal endocarditis The sensitivity of this procedure however, in diagnosing patients with IE is relatively poor In one study, only one third of patients with clinically and bacteriologically documented IE had positive results[12] Echocardiography does not distinguish between active and inactive cases,[11] and false positive results may occur[13]

Echocardiography is also useful as a prognostic indicator and may identify patients who require surgical intervention Individuals with IE who have vegetations large enough to be documented by this technique have a poor prognosis These patients more frequently require surgery for congestive heart failure and have higher mortality rates than those without this finding[1] There is also a strong association between the presence of vegetations on echocardiography and embolic phenomena[12] Premature closure of the mitral valve in IE with acute aortic insufficiency is demonstrated by echocardiography and is associated with a poor prognosis[1] This finding may indicate the need for early valve replacement Echocardiography indicates the nature of the pre existing cardiac lesion in up to one half of cases[13] It also may define the extent and nature of damage secondary to the infectious process[1] This and other information provided is important when surgical intervention is being considered

Cardiac catheterization

Cardiac catheterization of patients with IE may document unusual or clinically unsuspected intracardiac complications define the extent and

hemodynamic significance of valve damage or identify the infected valve

In patients with active endocarditis quantitative differences in bacterial counts done on samples obtained through catheters from sites proximal and distal to the suspected lesion may indicate the site of infection This technique may be most useful in right sided endocarditis where murmurs indicating tricuspid or pulmonary valvulitis are often absent [6] In patients with endocarditis who deteriorate despite medical therapy immediate valve replacement may be indicated Cardiac catheterization with cineangiography has been useful in these patients in demonstrating complications such as mycotic aneurysms or ventricular septal defects

Patients with residual valvular damage may also benefit from catheterization prior to surgery A retrospective study of 19 patients with bacteriologically inactive endocarditis was recently reported by Mills and associates [1] In this study catheterization with cineangiography was performed to clarify an uncertain diagnosis or to confirm a diagnosis suspected on clinical grounds Direct inspection at the time of cardiac surgery or pathologic examination was used to document the anatomical diagnoses Catheterization was often useful when the diagnosis was unclear Three patients were thought to have combined mitral and aortic insufficiency The severity of each lesion could be determined in two and the third patient was shown not to have mitral insufficiency The clinical diagnosis of mitral stenosis in two patients was shown by catheterization to be incorrect The relative contribution of valvular insufficiency to heart failure was determined in two patients one with emphysema and another with pericarditis

Two serious complications resulted from these studies One patient developed pulmonary edema and another a fatal arrhythmia Bacterial vegetations were not demonstrated in any patient by cineangiography and four patients had false positive tests indicating valvular insufficiency In patients with clear cut mitral insufficiency, catheterization data provided little additional information Paravalvular lesions (five mycotic aneurysms and one fistulous tract) were present in six patients Cineangiography demonstrated only three of these defects These authors conclude that cardiac catheterization is helpful when several valves are involved with infection when a paravalvular lesion is present or to determine the relative contribution of valvular insufficiency to heart failure

Serologic tests

Serologic tests used in the assessment of patients with IE can be divided into those which suggest a particular etiologic agent or myocardial involvement and those tests which show a heightened immunologic state Serologic tests may be useful in diagnosis of culture negative endocarditis and in following the course of therapy

Rheumatoid factor (RF) is present in the blood of approximately 50 per cent of patients with IE in whom symptoms have been present for six weeks or more RF is an IgM directed against the Fc portion of IgG and its presence may interfere with IgG mediated opsonization of bacteria The presence of RF correlates with active disease and titers fall rapidly with adequate therapy

The presence of glomerulonephritis due to the deposition of immune complexes has been found with IE of a number of bacterial etiologies A recent paper documenting the presence of circulating immune complexes (CIC) in patients with IE is of considerable interest The possible diagnostic value of this test in culture negative endocarditis has been stressed In this study 97 per cent of cases with IE had circulating immune complexes as compared to 10 to 40 per cent of control groups Moreover the patients with CIC unrelated to endocarditis had lower titers than those with endocarditis As with RF titers of CIC are related to duration of disease Although titers do diminish with adequate therapy persistent CIC levels do not necessarily indicate a poor therapeutic response The sensitivity of this test was better than that of the simpler measurement of complement levels the latter being decreased in only 41 per cent of cases of IE Tests which measure CIC have potential usefulness in culture negative endocarditis but these tests are difficult to perform and are not available in most laboratories

Tests used for the determination of specific etiologic agents include those which demonstrate the presence of an antibody directly such as immunoprecipitation tests and complement fixation tests

inactivate antibiotics which may have been carried over into the culture flask from the patient's blood The addition of a beta lactamase (penicillinase) to the medium may be helpful in patients who have received penicillins or cephalosporins Care should be taken not to over inoculate the blood culture bottle Antibiotics in the blood will be diluted by the larger volume of liquid culture medium, decreasing their activity The presence of cell wall deficient forms should be sought in patients who have received agents whose primary activity is on the cell wall Such drugs include the penicillins, cephalosporins and vancomycin Since cell wall deficient forms of bacteria will not grow on ordinary media, a hypertonic medium such as broth with 10 per cent sucrose should be used in addition to the routine blood culture bottles Organisms requiring special growth factors not present in standard media are sometimes seen on Gram stain from patients with IE The use of enriched medium may permit the isolation of these organisms[8] Although thioglycollate or other anaerobic blood culture media will usually support the growth of anaerobes routine subculturing and the incubation of bottles for many days are especially important when anaerobic endocarditis is suspected Patients with gastrointestinal disease or prosthetic valve endocarditis account for most cases of anaerobic IE Fungal endocarditis is another important cause of culture negative endocarditis Candida species are more often associated with positive cultures than other fungi such as histoplasma or aspergillus species The fungemia associated with candida endocarditis may not be continuous and often many days are required for the isolation of this pathogen The use of biphasic medium and the aeration of bottles facilitate the isolation of these pathogens Routine aeration of one bottle may also facilitate the isolation of some bacteria such as pseudomonas species Fungal endocarditis should be suspected in the presence of drug addiction following prosthetic valve replacement and in patients with intravenous or urinary catheters who have received parenteral antibiotic therapy The presence of large emboli in culture negative IE also suggest a fungal etiology and the histologic and bacteriologic examination of material removed at embolectomy may provide a diagnosis

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Cardiac catheterization

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abnormality may have some localizing value[25]

One recent study correlated pathologic findings with ECG abnormalities in 24 patients with IE involving the aortic valve[26] Eighteen of 24 patients with aortic valve endocarditis had prolonged P R intervals unrelated to digitalis Four developed complete heart block Deep infection with aneurysm formation was present in 16 of these 18 patients Four patients who developed left bundle branch block with normal P R intervals had aneurysms of the intraventricular septum Four of 24 patients had evidence of a myocardial infarction with multifocal ventricular ectopic beats and two of these had coronary artery emboli on postmortem examination

It is important to obtain serial ECG s in patients with the diagnosis of infective endocarditis Electrocardiographic evidence of an infarction or heart block is associated with a poor prognosis New conduction defects indicate abscess or aneurysm formation and may suggest the need for surgical intervention

Conclusions

The rational use of techniques introduced in the past several years for assessing patients with suspected or proven IF requires careful patient selection With the exception of cardiac catheterization these tests are noninvasive and therefore not associated with significant morbidity The general availability of many of these tests is limited and the sensitivity and/or specificity may be less than more conventional studies Serologic studies measuring circulating immune complexes teichoic acid antibodies and antiheart antibodies often require the sending of samples to reference laboratories Gallium scans cardiac catheterization and echocardiography may require the transfer of patients to hospitals with facilities for such studies Despite these limitations the use of one or more of these tests in individual patients may provide information crucial to the diagnosis or management of patients with infective endocarditis

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Staphylococcus aureus cell walls contain the antigenic moiety ribitol teichoic acid The determination of an antibody response to teichoic acid using immunoprecipitation tests such as counter immunoelectrophoresis (CIE) or double diffusion in agar may be useful in patients with IE due to this organism CIE is more rapid and sensitive than agar diffusion and has been proposed as an aid to early diagnosis of this infection [9] The latter is relatively sensitive and more specific than the CIE These tests have most potential usefulness in patients who have received antibiotics active against *Staphylococcus aureus* In some studies antibodies to teichoic acid may be found in as many as 90 per cent of patients with IE due to this organism There is a correlation with adequate therapeutic response and fall in titer A number of problems exist with this diagnostic test Teichoic acid antibodies may be found in uninfected drug addicts and the presence of antibodies does not necessarily indicate endocarditis in patients with staphylococcal sepsis [1] False positives occur in some patients with IE due to a streptococcal species [9] Furthermore, the absence of a standardized commercially available antigen limits the availability of this test

Serologic tests may also be useful in cases of culture negative fungal endocarditis In patients with Candida endocarditis blood cultures will be positive in 50 to 75 per cent of cases Serologic tests include immunoprecipitation and agglutination The usefulness of these serologic tests has been questioned since significant titers may occur in noninvasive disease and false negatives may occur in invasive candida infection

In patients in whom the clinical diagnosis of endocarditis due to candida is suspected serologic tests may give additional supportive evidence especially when combined with echocardiography Serologic studies available for the diagnosis of less common fungal etiologies such as aspergillus or histoplasma species are of limited use As with candida infections a single high titer or a changing titer may be helpful in certain circumstances

Coxiella burneti the agent of Q fever is an unusual cause of infective endocarditis and may be suspected in patients with culture negative disease where there is a history of animal contact [1] An increase in the complement fixing antibody titer is required to diagnose this infection Similarly, Brucella species may cause culture negative endocarditis in patients with animal exposure and may be diagnosed serologically

The presence of antiheart antibodies measured by indirect immunofluorescence has been reported in nine out of 13 (62 per cent) patients with subacute endocarditis [3] Antibody titers were associated with congestive heart failure and titers fell with adequate therapy Antiheart antibodies may be seen in a variety of cardiac disorders and this test is unlikely to be useful in diagnosing or following patients with endocarditis

Gallium scans

The radiopharmaceutical Gallium 67 citrate localizes in areas of inflammation and in many neoplasms Scintigraphy with gallium may be helpful in localizing occult infective foci such as intra abdominal abscesses This diagnostic procedure has recently been evaluated in ten patients with acute bacterial endocarditis and in an additional patient with a myocardial abscess [4] Scanning demonstrated accumulation of the isotope within the heart in six of the IE cases and in the single patient with a myocardial abscess The resolution of this procedure is not sufficient to determine which valve is infected and there is a delay of at least 48 hours before scans become positive With 40 per cent false negative results the sensitivity of this procedure is considerably less than blood cultures The potential usefulness of gallium scans in patients with subacute infective endocarditis or culture negative endocarditis has not been determined

Electrocardiography

The relative importance of the electrocardiogram (ECG) in the assessment of patients with IE has recently been stressed [5] However there has been no comprehensive study of ECGs in patients with this infection ECG changes are not diagnostic of endocarditis and often consist of partial or complete heart blocks and premature ventricular contractions indicating myocarditis or the involvement of the conduction system with infection or inflammation The anatomical relation of the non coronary cusp of the aortic valve and the mitral annulus with the conduction system accounts for the frequency of conduction abnormalities and the type of the conduction

Annotations

Preventing thromboembolism after myocardial infarction
Effect of low dose heparin or smoking

When patients with myocardial infarction were kept in bed for several weeks thromboembolic complications were thought to be the casue of death in some 4 per cent of patients. Although most cardiologists think that such complications are less common now that patients with myocardial infarction are mobilized more quickly a third of such patients still develop evidence of leg vein thrombosis, as detected by the I fibrinogen uptake test and a proportion of these undoubtedly develop fatal pulmonary embolism Another serious thromboembolic complication is cerebral embolism from thrombi on the ventricular wall

It is recognized that heparin therapy in full dosage effectively prevents thromboembolic complications after myocardial infarction but this benefit has to be weighed against the possible hemorrhagic complications of the treatment Studies which were undertaken to defin those patients in whom the risk of thromboembolism would be greater than the risk of the hemorrhagic complications of the anticoagulant therapy indicated not unexpectedly that thromboembolic complications were more likely in the elderly in those in heart failure and in those with a significant dysrhythmia Unexpectedly it was also found that leg vein thrombosis after myocardial infarction was significantly more common in non-smokers than in smokers

Deciding which patients should be given full dose heparin prophylaxis was a nice exercise in clinical judgment to which the technique of decision theory has been applied but these niceties of clinical decision making have been made less nece sary by the advent of low dose heparin prophylaxis This has been shown to be effective in preventing thromboembolic complications after surgery and several studies have now shown that low dose heparin prophylaxis is also effective in preventing leg vein thrombosis and so presumably pulmonary embolism after myocardial infarction

The lower incidence of leg vein thrombosis after myocardial infarction in smokers compared to non smokers is the first reported health ben fit of smoking It is a dubious one however because the smoker is more likely to be suffering from a myocardial infarction in the first place

Why being a cigarette smoker should confirm any protection against leg vein thrombosis after myocardial infar tion is not known It is interesting that a decreased incidence of leg vein thrombosis has al.o been reported in smokers after gynecologi al operations

One pos ble explanation is that smokers are likely to be more fidgety people especially when they have had to stop smok ng after admission to a coronary care unit and start their own involuntary postoperative or postmyocardial infarction mobil zation earlier

The practical conclusion to be drawn from these observations is that low-dose heparin prophylaxis should probably be given to all patients with myocardial infarction and certainly to those with an increased risk of thromboembolic complications that is the elderly those with varicose veins or a previous history of thromboembolism those in cardiac failure or a dysrhythmia and those who are non-smokers Five thousand units of heparin are given intravenously and 7,500 subcutaneously as soon as possible after diagnosis and then 7 500 units subcutaneously every 12 hours until the patient is mobilized

The only disadvantages of giving low-dose heparin prophylaxis are the cost and trouble and the occasional problem of bruising at the subcutaneous injection sites Such bruising can be minimized by careful attention to the injection technique Seven thousand five hundred units of heparin in 0 3 ml is drawn up into a tuberculin syringe and injected subcutaneously into the anterior abdominal wall near the iliac crest using a new fine gau e needle i e not the one which was used for drawing up the heparin The nurses should be told to insert the needle vertically and to resist their overwhelming instinct to rub the site of the injection There is evidence from a small controlled trial that calcium heparin is less likely to cause bruising than sodium heparin but the difference is probably marginal.

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One possible explanation is that smokers are likely to be more fidgety people especially when they have had to stop smoking after admission to a coronary care unit and start their own involuntary postoperative or postmyocardial infarction mobilization earlier

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The only disadvantages of giving low-dose heparin prophylaxis are the cost and trouble and the occasional problem of bruising at the subcutaneous injection sites Such bruising can be minimized by careful attention to the injection technique Seven thousand five hundred units of heparin in 0 3 ml is drawn up into a tuberculin syringe and inj cted subcutaneously into the anterior abdominal wall near the iliac crest using a new fine gauge needle i e not the one which was used for drawing up the heparin The nurses should be told to insert the needle vertically and to resist their overwhelming instinct to rub the site of the injection There is evidence from a small controlled trial that cal ium heparin is less likely to cause bruising than sodium heparin but the difference is probably marginal

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Of how non-invasive *is* non-invasive?

When a treadmill exercise test is obtained along with echocardiogram (ECHO) Holter monitoring vectorcardiogram (VCG) apexcardiogram carotid pulse tracing and jugular phlebogram as well as with routine urinalysis ECG EPA of the chest SMA 12 and often repeats of the same etc the special procedures are considered non invasive But how non invasive are they psychologically and economically? All experienced physicians know how disturbing the mere mention of the existence of a slight murmur can be to a patient Some patients never recover from such a casual remark Unfortunately the terms invasive and non invasive are now used and interpreted to mean only physical invasion This is inadequate consideration People have minds too Disturbance of mind and thought can be even more troublesome crippling and invasive than casual consideration might suggest Remember always patients are people with *minds* as well as bodies And finally remember that the unnecessary use of these non invasive studies definitely *does invade* the pocketbook

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Another link between the left stellate ganglion and the long Q-T syndrome

Electrical alternation of the T wave associated with emotional or physical stress is characteristic of the long Q T syndrome and often precedes life threatening arrhythmias This phenomenon has been experimentally reproduced in animals by stimulating the left stellate ganglion Moreover blockade of the right stellate ganglion which permits dominance of the left cardiac sympathetics not only lengthened the Q T interval in long Q T syndrome but also evoked T wave alternans and ventricular arrhythmias Excessive sympathetic stimulation of the heart via the left stellate ganglion resulting from a congenitally low activity of the right cardiac sympathetic nerves has been suggested as the pathogenetic mechanism The important role of the left stellate ganglion in cardiac arrhythmias has been recently demonstrated Furthermore in a patient with long Q T syndrome at left stellectomy after failure of medical treatment manipulation of the left stellate ganglion consistently produced ventricular tachycardia thus confirming this ganglion s modulation of dangerous ventricular arrhythmias This report describes temporary abolition of T wave alternation during blockade of the left stellate ganglion in a patient with Romano Ward syndrome

A 26 year old white housewife had fainted two to three times yearly for 15 years during pleasant and unpleasant emotion After negative neurologic and EEG examination at age 20 she took phenytoin for a time At age 21 she fainted upon hearing in the next room the voice of an old friend who had visited unexpectedly Before each faint she noted heart pounding and had the urge to run away Asymptomatic long Q Tc interval was found in the patient s mother (0 [illegible]2 sec) maternal grandmother (0 47 sec) and son (0 47 sec) In the patient s sister (0 4[illegible] sec) and father (0 44 sec) Q Tc was normal Another maternal uncle and his son had childhood syncope which disappeared in adult life Three maternal aunts died suddenly at 2 years at 30 years with childhood cyanosis and at 33 years in sleep with presumed brain hemorrhage At age 23 after uneventful induced labor for toxemia of pregnancy at another hospital the patient was abruptly separated from her newborn son because of suspected tuberculosis She lapsed into hysteria fainted and convulsed whenever she

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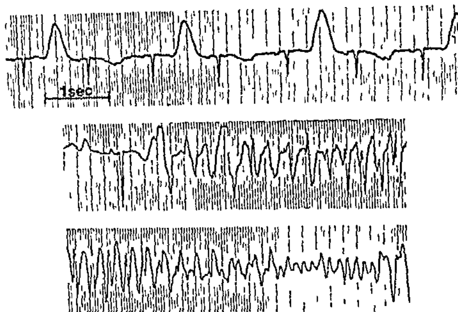


Fig 1 *Upper* precordial bipolar lead shows Q T interval alternans of 0 8 and 0 61 sec and T wave alternans of opposite polarity which preceded ventricular tachycardia *Center and lower panels* continuously record ventricular R-on T ectopy tachycardia and transient fibrillation succeeding another episode of Q T and T alternans.

heard babies brought to other mothers to nurse She became cyanotic and pulseless with dilated pupils and required DC shock for ventricular defibrillation R-on T ventricular ectopy was then identified during hysterics Although the first serum potassium was 3 4 and calcium 3 9 mEq /L these rose to 4 6 and 4.8 mEq /L with treatment while the Q T interval remained prolonged Treatment also included lidocaine and propranolol After each of six episodes of alternans of the Q T interval and T wave she had ventricular ectopy tachycardia flutter or fibrillation (Fig 1) She also had paroxysmal A V junctional tachycardia Upon entry to this hospital the cardiovascular examination serum electrolytes and echocardiogram were normal but Q T interval and T wave alternans prolonged Q T interval, and occasional ventricular ectopy were seen Although left stellate ganglion blockade with 8 ml of 1 per cent lidocaine induced left Horner's syndrome suppressed alternation of the Q T interval and T wave and shortened the Q T interval to a constant value alternans reappeared 16 hours after blockade (Fig 2) After 24 hours of propranolol and phenytoin treatment the T wave alternans disappeared A 24 hour ECG tape showed prolonged Q T interval but no alternans of Q T and T wave and no ventricular ectopy The husband was taught basic life support During the ensuing 3 years she has never fainted she takes extra propranolol 40 mg for palpitation The Q Tc has ranged from 0 49 to 0 52 sec during daily propranolol 120 to 160 mg and phenytoin 300 to 400 mg therapy Recently when a late systolic murmur without click appeared a second echocardiogram showed prolapse of the posterior mitral leaflet An audiogram was normal

The abolition of T wave alternation during left stellate blockade and its later return in the present case together with the production of T wave alternans by both stimulation of the left stellate ganglion in animals and by blockade of the right stellate ganglion in man demonstrates the crucial role of the left stellate ganglion in this phenomenon The left stellate ganglion has been successfully excised to prevent syncope ventricular fibrillation and death in 11 cases of long Q T syndrome The prospective assessment of the influence of left

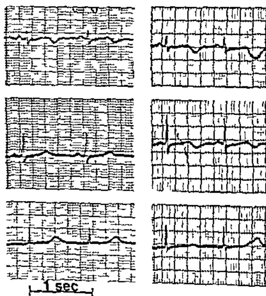


Fig 2 *Left panels* show Leads I II and III after left stellate blockade shortened Q T from 0.59 to 0.52 sec *Right panels* simultaneously record Leads I II and III with Q T interval alternans of 0.55 and 0 67 sec and T wave alternans of 0 2 and 0 4 mV 16 hours after left stellat blockade (1 mV = 1 cm.)

stellate blockade and subsequent antisympathetic drug treatment may assist in identifying first those patients in whom the left stellate ganglion clearly modulates dangerous arrhythmias Second the disappearance of T wave alternans during increasing doses of propranolol and phenytoin supports the antisympathetic merit of these drugs in long Q T syndrome The rationale for excision of the left stellate ganglion as specific therapy for long Q T syndrome is supported by the finding that left stellectomy raises the threshold for ventricular fibrillation i e it reduces vulnerability to ventricular fibrillation The suppression of alternation of the T wave one of the characteristic ECG signs of long Q T syndrome[1] by blockade of the left stellate ganglion links this ganglion again to an imbalanced cardiac sympathetic innervation with left dominance as the major pathogenetic mechanism for the syncope and ventricular arrhythmias seen in long Q T syndrome and possibly for the long Q T syndrome itself

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Roll over test

The etiology of hypertension induced by pregnancy is unknown Recently several papers have suggested that the possible mechanism for hypertension may involve factors that regulate the utero-placental blood flow The utero-placental unit represents a system in which blood flow is highly critical *It would seem logical to search for a self regulatory* hemodynamic mechanism such as that demonstrated in the renin-angiotensin-prostaglandin regulatory mechanism in *the kidney*

One hundred randomly selected normal primagravida women between 28 and 32 weeks gestation were subjected to the roll over test as described by Gant and associates The patient was placed in the left lateral recumbent position and a blood pressure was taken at 5 minutes and again at 15 minutes The subject was then turned to the supine position and the blood pressure was measured immediately and 5 minutes later with the patient still supine An increase in diastolic pressure of 20 mm Hg or more was considered a positive roll over test Auscultatory blood pressure measurements utilizing the onset of the first (systolic) and fifth (diastolic) sounds of Korotkoff were used when recording the blood pressure

Twenty five women had a positive test Thirteen of those 25 women developed pre-eclampsia requiring magnesium sulfate therapy Eight had transient hypertension during labor requiring no therapy Four had no evidence of hypertension during pregnancy A false positive rate for the 25 women with a positive "roll over test" was 16 per cent Seventy five women had a negative roll over test Sixty-eight of those women had no evidence of hypertension of pregnancy Seven had evidence of transient hypertension during labor requiring no therapy A false negative test was present in 10 per cent of the 75 patients with a negative roll over test In no case did a patient with a negative test develop pre eclampsia The roll over test" is recommended *as a routine test for every pregnant* patient between 28 and 32 weeks gestation for the early diagnosis of hypertension of pregnancy

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Letters to the Editor

Dissertation on a Roast Pig Updated

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Consider the following points

1 Even ordinary abdominal and pelvic surgical procedures are associated with a small but *appreciable incidence of acute* myocardial infarction in the perioperative period

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7 Myocardial infarction during or following cardiac surgery occurs in a setting unusually favorable for survival The vital signs are continuously monitored and maintained at hemodynamically optimal levels Adequate oxygenation is assured *Fear and pain are dampened (and thus the release of* catecholamines diminished) by analgesics and soporifics The slightest unfavorable turn is *instantly detected by the ever* vigilant medical and nursing staffs and appropriate corrective measures taken No physical activity of any kind is permitted Such an ideally controlled environment stands in contradistinction to the chaos that follows those crucial but medically unattended first few hours following a myocardial infarction at home Such a difference very well may explain the mordinately low *perioperative mortality rate of acute myocardial* infarction complicating cardiac surgery

Considering *all of these factors one is led to speculate that* coronary bypass surgery may accomplish the relief of angina pectoris not so much by improving coronary perfusion (which of course may be an added benefit) but primarily by inducing a relatively benign form of myocardial infarction Conceivably by converting electrically unstable ischemic tissue to electrically inert infarcted myocardium the incidence of arrhthmias may be reduced and survival increased too If the induction of *controlled myocardial infarction indeed is the* mechanism surely there must be a better way to accomplish this same end!

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Setting the record straight on TAPVC

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I don t understand the *term* research trainee that Dr Rathnam uses that itself is a misstatement of fact Dr Bharati is the *Associate Director of the Congenital Heart* Disease Research and Training Center

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More on jugular venous pulse (JVP) tracings and cannon waves

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We have read with interest the paper by Drs Berman and Waxman (AM HEART J 91 643 1976) drawing attention to the diagnostic value of the jugular venous pulse tracings (JVP) in cardiac arrhythmias. JVP is a sensitive and non invasive method in detecting P waves concealed in the T wave and especially in the QRS complex Cannon waves can be frequently observed in sinus tachycardia with prolonged atrioventricular (A V) conduction time atrial tachycardia atrial flutter all junctional rhythm disturbances ventricular extrasystoles ventricular tachycardia and ventricular escape rhythm

We agree with *the authors that cannon waves are not* commonly produced in A V association due to sinus tachycardia with first degree A V *block This is even more true for*

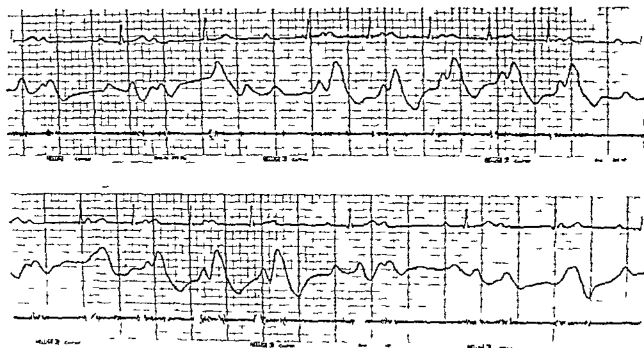


Fig 1 *Top and bottom* ECG Lead II JVP and phonocardiogram tracings from 54 year-old male patient with moderate aortic regurgitation and 1st degree A V block accompanied by frequent episodes of high grade A V block

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Returning to Drs. Berman and Waxman s case we can find no hemodynamic cause responsible for the increase in amplitude of wave 12 called a small cannon wave by the authors

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Additional angiocardiograms for Tetralogy of Fallot

To the Editor

In the majority of children with tetralogy of Fallot a good quality biplane right ventricular angiocardiogram or cineangiocardiogram is adequate for definition of anatomy At times however due to presence of additional anomalies a more special projection will have to be obtained In our institution we have studied 325 children with tetralogy of Fallot in a 3½ year period and despite adequate preoperative biplane angiocardiograms in four instances the following anomalies were discovered during surgery origin of the right pulmonary artery from the ascending aorta origin of the right pulmonary artery from the descending aorta interrupted left pulmonary artery at the hilus of the lung and absent pulmonic valve with supravalvar pulmonic stenosis To avoid unpleasant surprises we have concluded that additional angiocardiograms from aortic root left ventricle and 40-degree elevated left anterior oblique (LAO) right ventricular projection must be obtained As it is obviously impractical to subject all children with the diagnosis of tetralogy of Fallot to all of the above studies we therefore recommend the following guidelines

In all cases of tetralogy one must primarily obtain a good quality biplane right ventricular angiocardiogram (or cineangiocardiogram) and while the child is still on the table the following points must be ascertained

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3 Main pulmonary artery and right and left branches must be seen in sequence with equal concentration of contrast material and continuous with each other

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5 It is mandatory to locate both semilunar valves

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Although institutional policies may differ we believe that if all the above points are checked out with certainty additional

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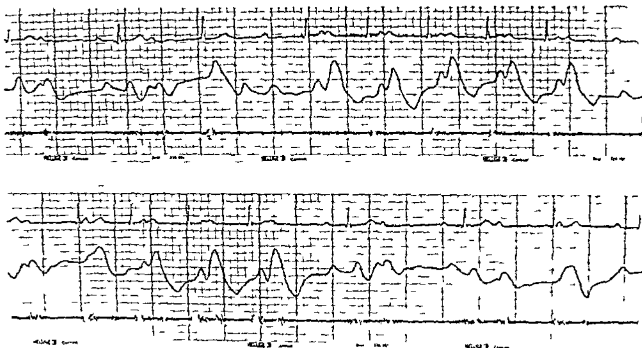


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Setting the record straight on TAPVC

To the Editor

I was surprised to read the letter of Dr Allen Rathnam in the May 1977 issue of the Journal (AM HEART J 93 676 1977) regarding the exchange of letters between Dr Bharati and Dr Van Praagh concerning TAPVC I do not ordinarily engage in polemics as I believe this is a waste of time But the remarks of Dr Rathnam are ill advised and I believe he has missed the main point of Dr Bharati s remarks to Dr Van Praagh

Dr Van Praagh said in his paper that This is the largest series of TAPVC published to date This was a misstatement of fact Of course any author can choose any references he or she wants to quote in his or her paper but he or she must not misstate a fact And of course Dr Van Praagh as a gentleman and scientist saw the point and said so

I don t understand the term research trainee that Dr Rathnam uses that itself is a misstatement of fact Dr Bharati is the Associate Director of the Congenital Heart Disease Research and Training Center

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More on jugular venous pulse (JVP) tracings and cannon waves

To the Editor

We have read with interest the paper by Drs Berman and Waxman (AM HEART J 91 643 1976) drawing attention to the diagnostic value of the jugular venous pulse tracings (JVP) in cardiac arrhythmias JVP is a sensitive and non invasive method in detecting P waves concealed in the T wave and especially in the QRS complex Cannon waves can be frequently observed in sinus tachycardia with prolonged atrioventricular (A V) conduction time atrial tachycardia atrial flutter all junctional rhythm disturbances ventricular extrasystoles ventricular tachycardia and ventricular escape rhythm

We agree with the authors that cannon waves are not commonly produced in A V association due to sinus tachycardia with first degree A V block This is even more true for

Book reviews

Pregnancy Hypertension By Emanuel A Friedman M D and Raymond K Neff Sc D Littleton Massachusetts 1977 PSG Publishing Company Inc 400 pages. Price $40 00

This book is intended primarily for obstetricians and gynecologists but should interest internists general practitioners and cardiologists for many reasons The book provides the reader with the viewpoint of the obstetrician Hypertension is an important problem in itself Hypertension offers special difficulties in the pregnant patient The book al o summarizes very well the Collaborative Perinatal Project supported by the National Institute of Neurological Diseases and Blindness (now the National Institute of Neurological Diseases and Stroke) The book is primarily a statistical report concerning such variables as age risk factors diagnostic factors standards choice of groups interrelationship of variables during pregnancy Fourteen university hospital institutions participated initially and two discontinued pri r to completion of the study The practicing physician will find this to be a useful reference source but will find the book rather difficult to read even though it represents the results of an important and extensive study Unfortunately none of the lar e hospitals for the indigent patients were in luded in the study in pite of difficulties they would have brought to view

Medical statisticians will find this to be a useful source of information on hypertension and pregnancy The influence of drugs and other a pects of therapy for hypertension on the fetus and fetal mortality is another important aspect of the book Medical libraries of the world should include the book among their files Obstetricians and others who manage hypertension will want to own a copy for reference The data and statistical analyses are extensive and well presented.

Correlative Atlas of Vectorcardiograms and Electrocardiograms By Doctors C V Ramana Reddy and Lawrence A Gould New York 19 7 Futura Publishing Company 294 pages

Th tated purpose for the preparation of this book was to pro ide the reader with electrocardiograms and vectorcardiogram ecorded simultaneou ly from adults with various types of heart disease and to correlate those recordings with a clini al ummary of the pat ent To this end the authors have a hie ed their goal Thus, as he would in practice the reader is permitted to interpret the ECG and VCG together This approach is certainly the preferable one and illustrates how mu h the ECG and clinical findings contribute to the interpretation of the VCG The authors interpretation of the electrocardiograms and vectorcardiograms follow each clinical presentation

Although the first chapter deals with the normal vectorcardiogram and electrocardiogram it is not adequate preparation for proper understanding of the material presented in this book. Therefore the reader should acquaint himself with the fundamentals of VCG and ECG before reading the book

The illustrations are of good quality The Frank VCG lead system is used througho t the book. The appendices contain differential diagnoses of various vectorcardiographic patterns and would serve as a useful reference for analysis of complicated vectorcardiograms This book will be of value to trainees in cardiology and practising cardiologists and hopefully will stimulate clinicians to use electrocardiography and vectorcardiography in a complimentary fashion

Auscultation of the Heart third edition By Abe Ravin M D Lane D Craddock M D Phillip S Wolfe M D and David Shander M D Chicago 19 7 Year Book Medical Publishers Inc 285 pages

The third edition of *Auscultation of the Heart* contains the same fundamental principles of auscultation as the first edition and now includes the systolic click postoperative cardiac sounds and correlations with echocardiography Except for these additions, the third edition is essentially the same as the first This is surely expected for heart sounds are not expected to change nor is the use of the stethoscope The main shortcoming of this book is the failure to emphasize continuously for learners the relationship of the heart sounds to various simultaneous cardiac events, especially the hemodynamic events The relationship to the ECG is relatively simple and adequate for timing but heart sounds represent mechanical and hydraulic phenomena rather than electric For beginners, the importance of auscultation is not limited to the mere detection of the various sounds murmurs râles etc but an understanding of the situation responsible for them and in turn the clinical significance

The book contains a bri f discussion of sound the stethoscope graphic recording normal sounds and abnormal sounds as produced by arious types of cardiac di ease The authors have produced a useful book about a neglected subject That this book is useful and a success is attested by the fact that a third edition appears

The Hypertrophied Heart Edited by Prof Dr Ruthard Jacob Darmstadt 1977 Dr Dietrich Steinkopff Verlag 2?? pages.

This paperback volume contains the papers presented at the Erwin Riesch Symposium held in Tubingen in September 1976 The 33 brief papers produce a book of ?? pages The range of the discussions is wide b ing concerned primarily with the biochemistry physical chemistry morphology and physiologic correlations with cardiac hypertrophy and the normal myocardium The relation of ultrastructure of the sarcoma to myocardial contraction is discussed within the limits of existing knowledge This symposium not only summarizes very well the existin knowledge of myocardial hypertrophy but also indicates the limited information available The investigators plunge into a discus ion of myocardial hypertrophy but they fail to define it adequately This only atte ts to the extent of the problems involved Regardless this book contains a good collection of brief papers that should interest all physicians biochemists biophysicists morphologists and pathologists This is an interesting book to read and study Myocardial hypertrophy is an important and common problem in medicine



Fig. 1. Normal anteroposterior *(left)* and lateral *(right)* projections of the right ventricle seen in angiocardiogram of a patient with tetralogy of Fallot.



Fig. 2. Angiocardiographic view showing a 40 degree elevated LAO right ventricular projection in a patient with tetralogy of Fallot. See text for explanation.

angiocardiograms are not necessary. Nevertheless, in our opinion one is obliged to continue and complete the study if any of the points in the checklist cannot be satisfied with certainty or if any of the following points exist:

1. Uncertainty regarding the ventricular septum (left ventricular injection).
2. Major difference or discrepancy in the size or dye concentration of the main right or left pulmonary arteries (40 degree elevated LAO projection).
3. Suspicion of right, left and main pulmonary artery junctional stenosis (40 degree elevated LAO projection).
4. Reversed tapering of the right or left pulmonary artery branches (40 degree elevated LAO projection).
5. Main right or left pulmonary artery transverse diameter equal to or larger than the aortic root diameter above the sinus of Valsalva (aortic root injection and 40 degree elevated LAO projection).

The standard anteroposterior and lateral projections of the right ventricle in a patient with tetralogy of Fallot (Fig. 1) is compared with the 40 degree elevated LAO right ventricular projection in Fig. 2. Note that the main and left pulmonary artery junctional stenosis is not evident on the anteroposterior and lateral projections, whereas it is easily noted on the latter view (Fig. 2).

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American Heart Journal

August 1978 Volume 96 Number 2

Editorial

Coronary stenosis Ischemic or non-ischemic factor?

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An entity can be defined only when all the pertinent variants have been recognized and their meaning has been understood However the rule is to postulate most of our definitions on a limited number of often misinterpreted findings After all most of the history of medicine is the history of errors [1]

For millennia the earth remained the center of the universe—an unquestionable objective fact documented already from the first primitive man by looking every morning at the rise of the sun and its course from east to west A few by looking at the stars questioned this undeniable fact and despite the Inquisition were right Today a boy of the elementary school could present a lecture in the school of Padua circa 1500 confirming the well grounded hypothesis of Copernicus just by showing a slide of our planet seen from the moon

Every morning in the autopsy room we can see—as did Morgagni the first primitive pathologist again in Padua—atherosclerotic plaque stenosing the lumen of the coronary arteries in most of the people dying from so called coronary heart disease (CHD) This is an objective fact which led to the present definition of CHD namely an absolute or relative (to an increased metabolic demand) reduction of the nutrient flow to the myocardium The obvious corollary is that the coronary arteries are functionally speaking end arteries This is another well documented fact since CHD occurs even in the presence of collaterals as is demonstrable by cineangiography

Let us look at the stars for a moment attempting to profile as far as we can the universe of CHD in relation to its natural history The first need is a selection of pure cases which really belong to the CHD natural history trying to avoid the frequent error of including cases associated with other diseases (cardiac and non cardiac) or that have undergone surgery or have been exposed to too prolonged intensive care What are we observing in these cases? Pertinent findings or the results of an association or iatrogenic effects alias experimental pathologic models?

The second need for a correct valuation of the functional meaning of the lesions is to study a control population In spite of the obvious limitations at present only a postmortem investigation may achieve this goal In fact all the in vivo information belongs to a population selected by a disease For instance non CHD patients with *normal* coronary angiograms can not be considered as *controls* since the disease may change the CHD natural history

From the Consigli N zion d l R ch Pr gram n Pre ent e Medici e Ath roscl rosis Project R me C N R I t tuto d Fi logia Cl n c Med l S hool Un ersity of Pisa and Institut of P th log ical Anat my Med cal School, Un ers ty of M lano

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Books received

Malpractice A Trial Lawyer s Advice for Physicians By Walter G Alton Jr LL B Boston 1977 Little Brown & Company 230 pages Price $9 95

The Marathon Physiological Medical Epidemiological and Psychological Studies Edited by Paul Milvy New York 1977 New York Academy of Sciences 1090 pages Price $75 00

Doppler Ultrasonic Assessment of Venous Disease By Robert W Barnes M D Henry E Russel and Michael R Wilson Iowa City 1975 The University of Iowa Hospitals 232 pages

Periphere Angiodysplasien By Robert A Schobinger Berne Switzerland 1977 Hans Huber Publishers 262 pages Price 58 Swiss francs or 58 Deutschmarks

Moderne Kardiologie die Ischamische Herzkrankheit im Elektrokardiogramm By Rassouli A Parsi and Herbert Semmler Jena Germany 1977 VEB Gustav Fischer 157 pages

Announcements

XXIV annual meeting on Thrombosis and Haemostasis

The 24th annual meeting of the International Committee on Thrombosis and Haemostasis will be held at the University of Leuven Belgium on July 20 through 22 1978 The different subcommittees will meet on Thursday July 20 (morning and afternoon sessions) and on Saturday July 22 Thursday evening and Friday morning are devoted to plenary sessions on the design of clinical trials in thrombosis All meetings are open and interested physicians and scientists are welcome Further information and registration forms can be obtained from the office of the Secretary General Dr K M Brinkhous Preclinical Educational Bldg 228 H Chapel Hill N C 27514 or from Dr M Verstraete and Dr J Vermylen Center for Thrombosis and Vascular Research Dept of Medical Research Campus Gasthuisberg Herestraat 49 3000 Leuven Belgium

Vascular Disease course

A course entitled Vascular Disease—Mechanisms and the Basis for Therapy will be presented at Hilton Head South Carolina on August 16 through 19 1978 Co directors for the program are Robert Lefkowitz and Andrew Wallace sponsorship is by the Council on Clinical Cardiology of the American Heart Association For further information contact Administrator Postgraduate Programs American Heart Association 7320 Greenville Ave Dallas Texas 75231 Telephone (214) 750 5441

Circulation Annual Scientific Meeting

The Council on Circulation Annual Scientific Meeting will be held in Snowmass Colorado on August 17 through 21 1978 under the sponsorship of the Council on Circulation of the American Heart Association and the Colorado Heart Association Phillip Schmidt is course director For further information contact Administrator Postgraduate Programs American Heart Association 7320 Greenville Ave Dallas Texas 75231 Telephone (214) 750 5441

Third Canadian Summer Workshop in Electrocardiography

The Third Canadian Summer Workshop in Electrocardiography will be held at the Sheraton Centre Hotel Toronto Ontario Canada on July 3 through 7 1978 The workshop will be conducted by Henry J L Marriott M D of the Rogers Heart Foundation The workshop is acceptable for 21½ prescribed hours by A A F B and for credit toward Category 1 of the A M A Physician s Recognition Award Fee for the workshop is $125 U S funds For further information contact Program Chairman Rogers Heart Foundation St Anthony s Hospital St Petersburg Fla 33705 Telephone (813) 894 0790

Fifth European Congress of Anaesthesiology

The Vth European Congress of Anaesthesiology will be held in Paris France from September 4 through 9 1978 Title of the congress which will be held in the Palais des Congrès is Haemodynamics in Anaesthesia and Intensive Care For further details please contact Congres Anesthesie P M V B P 246 92205 Neuilly Sur Seine France

VI Asia Pacific Congress on Diseases of the Chest (The Heart and Lungs)

The VI Asia Pacific Congress on Diseases of the Chest dealing with medical and surgical aspects of heart and lung diseases and sponsored by the International Academy of Chest Physicians and Surgeons (Affiliate American College of Chest Physicians) will be held in Bombay India from November 18 to 22 1979 The Congress is being hosted by the Indian Chapters of the American College of Chest Physicians and will be organized by the Western India Chapter Many international physicians and surgeons in the field of heart and lung diseases will participate in the plenary sessions symposia and free papers For further information please contact Dr Aspi R Billimoria Secretary General VI APCDC L D Ruparel Medical Centre Dr Annie Besant Road Worli Bombay 400025 India

Table I Frequency of maximal lumen reduction

Source (No)	Lumen reduction (%)										Total			
	< 50		50 69		,0-79		80-89		≥ 90		≤ 69		≥ 70	
	No	%	No	%	No	%	No	%	No	%	No	%	No	%
AMI (70)	7	9 9	3	4 2	15	°1 4	°°	31 4	23	3 8	10	14	60	86
OMI (30)	1	3 3	0	0 0	5	16 6	5	16 6	19	63 3	1	3	29	97
SUD (95)	5	5 2	9	9 4	21	°2 1	26	27.3	34	35 7	14	15	81	85
SFD (10?)	1?	11.8	14	13 7	8	7 8	27	26 5	41	40 2	26	25	~6	75
NCA (100)	17	17 0	17	17 0	11	11 0	24	24 0	31	31 0	34	34	66	66
AD (97)	28	28 8	31	3 0	19	19 6	13	13 4	6	6 2	59	61	38	39

γ = 73 66 P < 0 001

Table II Frequency of severe stenosis (≥ 70%) vs number of main involved vessels

Source	≤ 69 ≥ 70		1		2		≥ 3		Total	
	No	%	No	%	No	%	No	%	No	%
AMI	10	14 3	28	40 0	24	34.3	8	11 4	70	100
OMI	1	3 3	10	33 3	12	40 0	7	23 3	30	100
SUD	14	14 /	39	41 1	26	27 4	16	16 8	95	100
SED	26	2.5	21	°0 1	27	26 5	28	°7 4	10?	100
NCA	34	34 0	26	26 0	18	18 0	22	22 0	100	100
AD	59	60 8	2'	22 7	13	13 4	3	3 1	97	100
Total	144	29 1	146	29 6	1°0	24.3	84	17 0	494	100

In all the groups the frequency of a stenosing plaque its degree of lumen reduction length and type (concentric eccentric and semilunar) as well as the behavior of the collaterals have been estimated[2,4]

From a study of this type the first main point in discussing the meaning of a plaque is the very high frequency of a severe stenosis in the control groups (Table I) 66 per cent of the non cardiac atherosclerotic patients (NCA) and 39 per cent of the normal people (AD) had at least one vessel with a lumen reduction higher than 70 per cent a frequency significantly inferior in respect of the CHD groups but nevertheless too high for a linear cause-effect relation between stenosis and ischemia In terms of lumen reduction per se the ischemic role of a severe stenosis becomes questionable as does any presumed cause which too often does not result in the expected effect This is particularly true if we note that a severe multi vessel involvement does not show any significant divergence between CHD and NCA groups and this also can be observed in the AD group (Table II) Even if the controls are regarded as possible CHD candidates if they had survived still the fact remains that at the time of death despite the severe coronary damage they were not CHD patients Furthermore it is very unlikely that in people living a normal life or stressed by a disease episodes of increased metabolic demand of the myocardium may not occur

Other findings which do not fit with the concept of a linear relation between stenosis and ischemia are

(1) In acute cases at the first episode (AMI and SED) death occurs independently from the degree of severe obstruction (same frequency of stenosis with different lumen reduction superior to 70 per cent) and the number of involved vessels (Table I and II)

(2) The lack of a relationship between the infarct size and the degree and number of the severe obstructive lesions (Tables III and IV) According to the classic view ischemia should be proportional to the grade of severity of the coronary damage and one would expect to find a maximal infarct size in the presence of severe multivessel involvement a supposition not confirmed by the facts

(3) Most of the cases already at the first episode show chronic even multiple obstructions preexisting from a long time (months or years) prior to the onset of the disease This is a long lasting clinically silent period in people living a normal stressful style of life

(4) Allowing for some discrepancies which will be discussed further no significant difference was noted as far as the length and types of stenosis in the different group was concerned All these

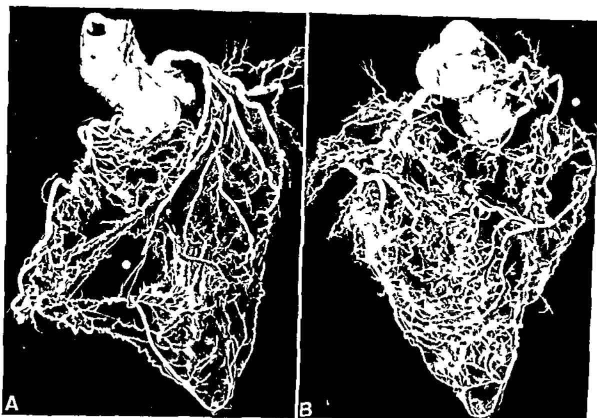


Fig 1 Cast of the coronary arteries *A* anterior view *B* posterior view Double occlusion (*o*) of the anterior descending branch and occlusion (*o*) of the right coronary artery in a 65 year old man without CHD and with normal myocardium Brain hemorrhage was the cause of death

The following selective criteria have been adopted in our study

1 *Acute myocardial infarct (AMI)* Subjects who die within 25 days from the onset of a clinically documented cardiac infarct with an unequivocal coagulation necrosis not associated with massive and extensive fibrosis As a histologic landmark of early coagulation necrosis only a polymorphonuclear cell infiltration was accepted Cases with other cardiac and non cardiac diseases as well as cases having undergone surgical procedure of any type or that had prolonged reanimation maneuvers were not included

2 *Old myocardial infarct (OMI)* People with the identical characteristics of the previous AMI group, but with the non healed coagulation necrosis associated with a massive scar with an extension greater than 5 per cent of the left ventricular mass Such an arbitrary distinction is suggested by the fact that a scar independent of its size is a non pathognomonic end result of any irreversible myocardial damage However it sounds reasonable to assume that a large scar in people dying from an acute infarct likely represents a previous one

3 *Sudden unexpected coronary death (SUD)* Apparently healthy subjects, in normal activity, without a history of CHD and other disease, who die suddenly (within 10 minutes) in the presence of witnesses and without medical assistance and reanimation attempts of any type The unique postmortem findings are atherosclerotic lesions of the coronary arteries and/or non inflammatory irreversible damage of the myocardium

4 *Sudden expected coronary death (SED)* Same as in the previous SUD group the only difference being a history of minor symptoms (episodes of mild chest pain dyspnea etc) retrospectively suggestive of a possible latent CHD

5 *Non cardiac atherosclerotic patients (NCA)* Patients who die from other non cardiac diseases (brain hemorrhage pneumonia etc) without history symptoms or signs of CHD and with normal myocardium

6 *Accidental death (AD)* Healthy people dying from violent death before any medical assistance without reanimation attempts and without a record of previous significant diseases as well as negative autopsy findings in the myocardium and other organs

epiphenomenon likely secondary to the infarct[7,8] On the other hand there is no morphofunctional proof that collaterals may suddenly lose their compensatory function as the primary event in infarct and sudden death Keeping in mind that by cineangiography a correct valuation of the anastomotic system is unobtainable[9] and that the capillary like makeup of these vascular structures does not support the concept of a possible spasm of the collaterals

A last argument seems worthy of discussion If we admit that at a certain critical point of lumen reduction/length a stenosis is bypassed by its own functioning anastomoses the same mechanism proposed for the secondary thrombus formation may explain the aggravation of a stenosis In fact the frequently observed progressive deposition of laminar mural thrombi within a plaque can be the result of the redistribution of flow by the collaterals Any time for any reasons an increased peripheral resistance in the depending vascular area ensues a further hypostasis within the stenosis (where there is already a critical hemodynamic situation because of the reduction of the proximal flow counterbalanced by the distal retrograde collateral flow) can be expected This hypostasis plus other thrombogenic factors (reduced fibrinolytic activity of the atherosclerotic wall irregular and serpiginous course of the stenotic lumen and others) may explain the secondary thrombus deposition A hypothesis supported by the frequent occlusion of a stenosis after an aortocoronary bypass the latter can be considered an equivalent of collaterals at very high pressure If so the worsening of a stenosing plaque becomes a meaningless fact in the ischemic sense The higher incidence of stenosis greater than 90 per cent in chronic patients (OMI Table I) the trend of triple vessel involvement in the latter (OMI and SED Table II) and the higher incidence of concentric plaque in infarcts may be more the secondary effects of the flow redistribution than the indication of an increased ischemia

In science the main needs are the discovery of new facts the discrimination between facts and appearances the formulation of well grounded working hypothesis and the admission of our ignorance Despite innumerous theories and proposed pathogenic factors CHD still is undefinable The natural histories of atherosclerosis and CHD are not synonymous Because of the collaterals the ischemic effects of the chronic stenosis as well as the acute event at its level seem more a preconceived postulate than an objective fact Obviously we have to explain why most of the CHD patients have severe atherosclerotic obstructive lesions the basic question being do we face a simple association or the atherosclerotic plaque act by an unknown mechanism On this subject long lasting controversies can be anticipated and these controversies are necessary with one condition that they do not become a tedious useless and often misleading repetition among people looking only at one image and not trying to see the universe We must keep in mind that CHD is a more complex phenomenon in which several pathogenic mechanisms are likely interacting as suggested by the different types of myocardial necrosis found in the disease[12]

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Table III Lack of correlation between the extension of *cardiac infarct (% total left ventricular* mass) and the degree of obstructive coronary damage

Lumen Reduction (%)	*No*	*< 49*			*50 69*			*≥ 70*			*Total*
Number of vessels	–	*1 (%)*	*2 (%)*	*3 (%)*	*1 (%)*	*2 (%)*	*3 (%)*	*1 (%)*	*2 (%)*	*3 (%)*	*%*
Infarct size (%)											
< 10	2 (7)	1 (3 5)	–	–	–	1 (3 5)	–	8 (27)	10 (34)	7 (24)	29 (100)
11 20	1 (5)	–	–	–	–	–	–	8 (40)	9 (45)	2 (10)	20 (100)
21 30	–	1 (4)	–	–	1 (4)	1 (4)	1 (4)	13 (52)	6 (24)	2 (8)	25 (100)
31 40	1 (9)	–	1 (9)	–	–	–	–	3 (27)	5 (45)	1 (9)	11 (100)
41 50	–	–	–	–	–	–	–	6 (50)	5 (41)	1 (8)	12 (100)
> 50	–	–	–	–	–	–	–	1 (33)	1 (33)	1 (33)	3 (100)
Total	4	2	1	–	1	2	1	39	36	14	100

Table IV Infarct size vs number of main coronary arterial vessels with severe stenosis

Infarct size (%)	*> 70% stenosis in*				*< 70% stenosis to*	
	1 (%)	*2 (%)*	*3 (%)*	*Total*	*normal*	*Total*
< 20	16 (32 6)	19 (38 7)	9 (18 3)	44	5 (10 0)	49 (100)
> 20	23 (45 0)	17 (33 3)	5 (9 8)	45	6 (11 7)	51 (100)
Total	39	36	14	89	11	100

0 2 < P < 0 3 χ = 2 49

conditions may be explained only by an adequate compensatory function of the collaterals

The continuously repeated claim is that the collaterals do not exist or are meaningless or cannot develop in time when needed The presence of anastomoses between the coronary arteries is no proof of their functional efficiency or readiness in an emergency The conditions which determine their responsiveness, particularly as far as time is concerned are at the moment still not adequately known [5] From one of the few solid experiment we know that in a relatively short time (less than one week) the normal collaterals may reach *a size capable of* compensating for a severe stenosis In fact the *occlusion of the latter is not followed by infarction* ventricular fibrillation electrographic changes or impairment of the cardiac dynamics By cineangiography and postmortem injection a dramatic increase in collateralization can be documented

From postmortem tridimensional casts of the *coronary* arteries we know that the normally existing collaterals (abundant everywhere) enlarge in diameter and increase in length in the presence of a severe obstruction These changes are proportional to the degree and number of the stenoses, independently of the presence or *absence of CHD In other words infarct* and sudden death cases show the same collateral enlargement as in non CHD subjects with the same degree of coronary damage This sounds logical since an anatomical structure (collateral network) responds to a functional stimulus (pressure gradient) on a physical basis This enlargement per se is already indicative of a compensatory function Furthermore all the previously *mentioned conditions (very frequent severe coronary* damage without CHD absence of correlation between degree/number of stenoses and mortality (and likely morbidity) as well as size of infarct pre clinical long lasting silent period) are the proof that collaterals are sufficient *and* behave in man as in the quoted experiments What does an emergency *mean in the natural* history of CHD? Is it a *vascular emergency* or something else? And if it is a vascular emergency by which mechanism? At present we know only that the infarct and sudden death cases occur

(1) With low frequency (about 7 per cent) in the absence of a demonstrable acute occlusion *and without or with minor atherosclerotic* lesions in no one instance is an occlusive thrombus seen in a normal artery

(2) In the presence (93 per cent) of severe often multivessel old obstructive damage associated *with highly enlarged* collaterals When found an acute occlusive factor (thrombus and/or rupture of atheroma plus intimal hemorrhage) is always located at the level of the severe stenosis and therefore apparently already bypassed by the *anastomotic flow This fact* suggested that the occlusive cause in this condition is a non effective

Studies of street drugs A total of 31 samples of drugs obtained from addicts were cultured on sheep blood agar and Sabouraud's medium in order to identify microbic contamination Included were seven samples of cocaine 12 samples of white heroin and 12 samples of brown heroin

Results

Of a total 80 cases of alleged endocarditis reviewed 42 were accepted as having infective endocarditis In 19 of the 42 cases there was an unequivocal history of parenteral drug abuse Eleven cases occurred in the year 1975 four in 1972 and two each in 1973 and 1974 Another 12 addicts were strongly suspected of having right sided endocarditis but failed to meet our criteria * An additional addict was seen in 1974 who had intravascular sepsis from the liver that mimicked right sided endocarditis

Ten (52 6 per cent) of the 19 cases in which endocarditis was linked to drug abuse were diagnosed clinically as having pure right sided (tricuspid) endocarditis Four patients had isolated aortic or mitral valve disease One patient (No 4) had had a mitral valve prosthesis implanted several years previously because of rheumatic valvular disease Two patients with underlying heart disease had been treated for subacute bacterial endocarditis due to alpha hemolytic streptococci several years earlier

Coagulase positive staphylococci were the etiological agents recovered in 13 (68 4 per cent) of our cases Candida species accounted for three (15 8 per cent) *Pseudomonas aeruginosa* was recovered in one patient (5 3 per cent) and two patients (10 5 per cent) showed *Streptococcus viridans* on repeated blood cultures In four of our 1975 patients with cultures positive for coagulase positive staphylococci the organism was sent to the Center for Disease Control Atlanta for phage typing Two of these organisms were classified as non typable one as 29 and one as WH1 The incidence of staphylococcal infection in 1975 showed no significant variation from the total incidence over the years reviewed (63 6 per cent vs 68 4 per cent)

Complications of the endocarditis seen among our patients included glomerulonephritis and uremia (one) hemiplegia (one) intracerebral

* Of these three occurred in 19"2 tw n 1973 tw in 19 4 a d 6 e n 19 5 (see T bl I)



Fig 1 Case No 13 Chest x ray on day of admission Diffuse bilateral infiltrates with possible necrotizing cavitation

bleeding (one) pericarditis (one) renal infarction and mesenteric occlusion (one) Osteomyelitis and mucopurulent conjunctivitis each occurred once in patients with staphylococcal endocarditis

A total of three (15 8 per cent) deaths occurred in our series Two of these (cases No 4 and No 6) were infected with Candida species and are discussed below The third patient had fulminating tricuspid endocarditis due to *Pseudomonas aeruginosa* Because of the fulminating course and the grave prognosis associated with right sided endocarditis due to this bacterium this case deserves special emphasis

Case reports

Case No 13 A 41 year old male was admitted on May 21 1975 with a 5-day history of fever cough with putrid sputum production and progressively increasing dyspnea He denied shaking chills hemoptysis or chest pain He admitted to drinking heavily and smoked one pack of cigarettes per day He stated that he had vomited several times during his illness He denied heroin use

Physical examination revealed an acutely ill male Vital signs showed respiratory rate 36/minute temperature 10° F heart rate 170/minute and blood pressure 140/90 mm Hg Cardiac auscultation revealed no murmur Auscultation of the chest showed scattered bilateral rhonchi with diminished breath sounds bilaterally over the bases

Total white blood count was 18 ,00/mm with 79 per cent

Infective endocarditis in heroin addicts Epidemiological observations and some unusual cases

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Infective endocarditis is a well recognized complication of parenteral drug abuse in which early diagnosis and prompt therapy leads to a significant decrease in mortality[8,9,11,13] It is generally accepted that pure tricuspid valve involvement is found to a significantly higher degree in parenteral drug users than in the non addict population[3,9] Coagulase positive staphylococci are the most frequently isolated etiological agents in the addict population with Gram negative organisms and candida species occurring regularly although less frequently[3,8,10,15,17,20]

It had been widely assumed that contamination of the illicit drugs during addition of diluting substances the use of non sterile diluent water the sharing of injection paraphernalia by several people without an attempt at sterilization between use and the egregiously unhygienic injection techniques of the addicts account for the high frequency of sepsis in the parenteral drug user[3,4,6] However, Tuazon and associates[16,18] studied 100 samples of street heroin and 100 items of injection paraphernalia obtained from infected addicts, and failed to isolate a single colony of staphylococci despite frequent isolation of other bacterial and fungal contaminants[16,18]

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Received for publication June 7 1977
Accepted for publication July 5 1977

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During the year 1975 we observed a significant increase in the number of heroin addicts with infective endocarditis in our hospital This increase appeared to coincide with the appearance in the street market of large quantities of 'brown heroin of Mexican and East Asian origin[21] We investigated the possibility of a relationship between our observed increase in the number of cases of endocarditis and the appearance of this new heroin source

Methods

Patient selection The medical records of all patients suspected of having infective endocarditis at Martland Medical Center Newark, N J were reviewed from January, 1972 through December, 1975 The records of all heroin addicts with evidence of sepsis admitted during the same time period were also reviewed In order to be included in our series as a bona fide addiction related case of infective endocarditis the following criteria had to be met (1) definite history of parenteral drug abuse, (2) multiple blood cultures growing the same organism (3) significant cardiac murmur or multiple pulmonary emboli on admission or developing during hospitalization and (4) oral temperature greater than 101° F (38 3° C) Organisms were identified by standard laboratory techniques Antibiotic susceptibility testing was done by the Kirby Bauer disc technique Minimum inhibitory concentrations by tube dilutions were obtained in several instances

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Table I Number of cases of endocarditis according to year of occurrence

Organism	1972	1973	1974	1975
Coagulase positive staphylococcus	4(2)	1	1(1)	7(3)
Candida		1	1	1
Pseudomonas				1(1)
Strep viridans				2
B hemolytic streptococcus		(1)		
No organism recovered	(1)		(1)	(1)
Total	4(3)	2(1)	2(2)	11(5)

Numbers in brackets ref to highly suspected but not defin tely onfirmed cases.

negative Serum hepatitis B antigen test was negative Anti nuclear antibody was present in a titer of 1 80 The electro cardiogram showed no abnormalities Chest x ray revealed small focal areas of opacity in both lung fields (see Fig 3) and lung scan showed multiple bilateral filling defects Three initial blood cultures were negative and repeated blood cultures over the next month (total ×17) were negative Sputum culture showed normal flora An intradermal test with intermediate PPD (5 T U) was positive but sputum showed no acid fast bacilli on smear or culture Liver scan was negative

During hospitalization afternoon temperatures daily rose to 101 to 105 6 F and chills persisted On July 8 1974 he coughed 75 c c of red frothy blood and complained of sharp left sided chest pain Auscultation revealed decreased breath sounds at the left base Cephalothin 3 Gm every 6 hours and gentamicin 80 mgm every 8 hours were given and this resulted in partial defervescence over the next five days but he continued to have pain and decreased breath sounds over the left chest A mid systolic click became audible at the apex The patient denied abdominal tenderness or pain High fever readings returned on July 14 1974 and continued daily thereafter Hemoptysis recurred on July 22 1974 Liver and bone marrow biopsies were performed and these showed no significant abnormalities and were negative on culture Chest x ray revealed focal bilateral nodular infiltrates some with central cavitation (Fig 4)

On July 25 1974 he experienced massive hemoptysis and died Autopsy revealed bilateral septic pulmonary emboli and abscesses. Heart and cardiac valves were normal but the liver showed multiple abscesses, the largest being 3 5 inches in diameter The largest abscess had eroded into the inferior vena cava and vegetations were found in this area within the inferior vena cava Cultures from aspirated pus of lung and liver abscesses yielded *Staphylococcus aureus*

Comment This to our knowledge is the first such case reported It is unique in two respects First staphylococcal liver abscesses have not been noted as a consequence of addiction Second despite multiple staphylococcal pulmonary emboli, all blood cultures using routine and hypertonic media were unrevealing This is surprising since the lung unlike the li er and spleen is ineffective in reducing microbial popula tions arri ing hematogenously When first seen by the arriving



Fig 4 Case No 20 Chest x ray three weeks after admission Several new fluffy infiltrates representing septic emboli have appeared

infectious disease team a diagnosis of tricu pid endocarditis probably due to *Staphylococcus aureus* was made However the negative cultures persistent fever increasing diffuse pulmonary infiltrates and positive tuberclin test prompted a presumptive diagnosis of disseminated tuberculosis Even in retro pect the correct diagnosis could not readily have been made Presumably a repeat liver scan in the face of the persistently elevated alkaline phosphatase and studies of serum antistaphylococcal antibodies might have been help ful

Of the three cases of Candida endocarditis one (No 4) developed infection with Candida parapsilosis on a mitral valve prosthesis and died before adequate therapy could be instituted The second (No 6) had previously documented rheumatic carditis with both aortic and mitral valve disease and had been treated successfully four years earlier for subacute bacterial endocarditis due to *Streptococcus viridans* This patient died during a surgical attempt to insert an aortic valve prosthesis He was found to have a large myocardial abscess extending from his aortic valve from which Candida species was recovered The third patient with Candida endo carditis (No 10) also had previously documented rheumatic heart disease She presented initially with a left sided hemiple gia Multiple blood cultures were positive for *Candida parapsilosis* The patient improved on amphotericin and 5 fluorocy tosine but left the hospital before finishing therapy Three weeks later she was readmitted again started on antifungal therapy and again signed out prematurely Six weeks later she returned complaining of fever and malaise Blood cultures at this time failed to show Candida Nevertheless antifungal therapy was again started and she felt improved After 4 weeks of therapy she again signed out against medical advice She



Fig 2 Case No 13 Chest x ray 72 hours after admission New fluffy infiltrates have developed bilaterally representing septic emboli

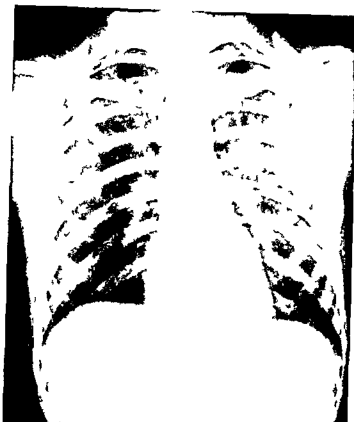


Fig 3 Case No 20 Chest x ray on day of admission showing bilateral infiltrates

neutrophils hematocrit was 47 per cent blood sugar 120 mgm per cent blood urea nitrogen 26 mgm per cent Alkaline phosphatase bilirubin and liver enzyme concentrations were all within normal limits Urinalysis was normal Blood gases revealed pO 34 4 mm Hg pCo 65 mm Hg HCO = 27 meg /L pH 7 24

Sputum gram stain showed many polymorphonuclear leukocytes with Gram positive cocci in pairs and chains and a few Gram negative rods Smears for acid fast bacilli were negative

ECG showed sinus tachycardia Chest x ray revealed diffuse bilateral infiltrates more pronounced on the right side (Fig 1)

The patient was intubated and given oxygen A presumptive diagnosis of aspiration pneumonia was made and treatment was started with clindamycin and gentamicin the latter being given because of the presence in sputum stain of gram negative rods On the third hospital day a repeat chest x ray showed new infiltrates in the upper lung fields (Fig 2) and the initial sputum specimens showed on culture normal flora plus a few pseudomonas organisms The patient was again queried about drug abuse and admitted to intermittent heroin use Blood cultures showed *Pseudomonas aeruginosa* and diagnosis of combined embolic and aspiration pneumonia was made Carbenicillin was added to the regimen but relentless deterioration continued On May 28 1975 he developed a pneumothorax and died Postmortem examination revealed right sided tricuspid endocarditis with multiple foci of embolic pneumonia

Comment This was a marvelously instructive case The history of alcoholism and the fetid sputum virtually established a diagnosis of aspiration pneumonia When new infiltrates appeared after hospitalization the possibility was entertained of continued aspiration in the hospital or iatrogenic pneumonia secondary to administration of oxygen via an apparatus with a reservoir nebulizer However the presence of pseudomonas organisms in the original sputum together with new infiltrates suggested the proper diagnosis of embolic pneumonia from vegetations on the tricuspid valve

The case of intravascular sepsis mimicking right sided endocarditis is so extraordinary it also merits particular emphasis

Case No 20 A 17 year old man was admitted on June 21 1974 with a 4 month history of intermittent chills night sweats non productive cough chest pain and 25 lbs weight loss He admitted using heroin for the past 4 years and had had four previous admissions for overdose since 1970 His chills developed in the evening occurred every 24 hours during the month prior to admission and were associated with left anterior chest pain leg pains and diaphoresis Physical examination revealed an acute and chronically ill appearing male Vital signs showed a rectal temperature of 101 heart rate of 108/minute respiratory rate of 24/minute and blood pressure of 110/72 mm Hg No cardiac murmur was audible and physical examination revealed no abnormalities

Laboratory studies showed a hemoglobin ranging from 10 1 to 7 2 gm per cent white blood count of 10 6 to 18 3 mm with a differential count of 84 per cent segmented cells 14 per cent lymphocytes and 2 per cent monocytes Alkaline phosphatase concentration was 116 international units per 100 ml Urinalysis L F cell preparation blood sugar smears for malaria and latex agglutination slide test for rheumatoid factor were

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Table II Endocarditis in heroin addicts

Case No	Age	Sex	Drug	Organism	Valve	Underlying disease	Presentation	Treatment	Outcome
1	26	F	Heroin	Staph C P	Tricuspid	None	Fever Hemoptysis Multiple pulm emboli Abscess of right antecubital fosse	Methicillin Vancomycin	Recovered
2	36	M	Heroin	Staph C P	Tricuspid	None	Fever Multiple pulm emboli	Methicillin Keflin	Recovered
3	46	M	Heroin	Staph C P	Tricuspid	None	Malaise fever Multiple pulm emboli and right sided effusion	Penicillin Methicillin Keflin	Recovered
4	17	M	Heroin	Candida nonalbicans	Mitral prosthesis	R H D age 8 Mitral valve prosthesis	Chills fever congestive heart failure	Keflin Gentamicin Amphotericin	Died
5	22	M	Heroin	Staph C P	Tricuspid	None	Chest pain & fever hemoptysis—RLL infiltrate & empyema	Keflin Clindamycin	Recovered
6	28	M	Heroin	Candida nonalbicans	Aortic	RHD with AI and MI 1970 SBE with strep viridans	Fever Left sided hemiplegia Osler node	Amphotericin B	Died during open heart surgery
7	24	M	Heroin	Staph C P	Tricuspid	None	Fever Septic emboli	Oxacillin Cefazolin	Improved Signed out against med advice
8	21	M	Heroin	Staph C P	Tricuspid	Diabetes	Fever chills cardiac murmur mucopurulent conjunctivitis	Cefazolin	Did well but had intermittent renal insufficiency
9	50	F	Heroin	Staph C P	Aortic & mitral	RHD hypertension cirrhosis SBE in 1971	Fever mental confusion Roth spots	Methicillin Cefazolin	Recovered in hospital developed renal infarct and mesenteric occlusion
10	26	F	Heroin	Candida	Aortic & mitral	RHD	Left hemiplegia harsh systolic & early diastolic murmur	Amphotericin B and 5 fluoro cystosine	Improved signed out against advice × 3 lost to followup

Abbreviations used CP = coagulase positive AMA = against medical advice RHD = rheumatic heart disease W = white B = brown AI = aortic insufficiency MI = mitral insufficiency SBE = subacute bacterial endocarditis IVC = inferior vena cava

was lost to follow up for the next 7 months at which time she returned for cardiac catheterization Although she had evidence of cardiac failure she had no fever and her erythrocyte sedimentation rate was 17 mm /hour (Westergren) Candida precipitins were negative whereas they had been positive during the first admission The echocardiogram showed damaged mitral and aortic valves but no evidence of any vegetations

The two patients with *Streptococcus viridans* endocarditis were a couple sharing both heroin and injection paraphernalia The husband was on hemodialysis for "heroin induced nephropathy and developed the endocarditis 4 months after he had started dialysis The wife had been hospitalized in 1972 with an intracranial hemorrhage No cardiac murmur was noted and cerebral arteriogram showed diffuse arterial spasm but no evidence of an aneurysm She was readmitted in 1975 in coma with a hemorrhagic cerebrospinal fluid This time the cerebral arteriogram demonstrated an aneurysm in the circle of Willis and cardiac auscultation showed an aortic insufficiency murmur The patient was treated successfully for her alpha streptococcal endocarditis and subsequently the cerebral aneurysm was removed surgically

Table II Continued

Case No	*Age*	*Sex*	*Drug*	*Organism*	*Valve*	*Underlying disease*	*Presentation*	*Treatment*	*Outcome*
11	25	F	Heroin	Staph C P	Tricuspid	None	Fever chills × 5 days multiple pulm emboli developed in hospital 3/6 syst murmur at left sternal border	Cephalothin and Gentamicin Cefazolin	Did well Cardiac cath. 5 months after cure showed pul regurgitation and mild tricuspid regurgitation
12	33	M	Heroin	Staph. C P from pericardial fluid and skin abscess	Tricuspid	Diabetes Obesity	Skin abscess × 2 wks Right axilla fever and rigors pleuritic pain & right pulm infiltrates	Cefazolin & Gentamicin	Pericardiectomy Died 1st day postop
13	44	M	Heroin	Pseudomonas aeruginosa	Tricuspid	None	Fever cough, pleural pain	Cefazolin Gentamicin	*Progression of pulmonary emboli* Died
14	17	M	Heroin	Staph C P	Aortic	None	Back pain & fever × 3 days Osteomyelitis of vertebrae	Oxacillin Cefazolin	Recovered
15	22	M	Heroin	Staph C P	Mitral	None	Fever & rigors splenomegaly 2/6 apical systolic murmur	Cefazolin	Improved—signed out against medical advice
16	34	M	Heroin	Staph C P	*Mitral*	RHD Alcoholism hyperten	Recurrent septic arthritis in L ankle	Cefazolin	Improved
17	31	M	Heroin Cocaine	Strep viridans	Aortic	Uraemic (on hemodialysis)	Fever *ascites* right pleural effusion	Streptomycin Penicillin	Recovered
18	25	F	Heroin	Strep viridans	Aortic	Intracranial hemorrhage 1971	Drowsy confused bloody CSF	Penicillin Streptomycin	Berry aneurysm successfully removed recovered
19	25	M	Heroin	Staph C P	*Tricuspid*	None	Fever multiple pulmonary emboli	Cefazolin Gentamicin	Improved—signed out against medical advice
20	17	M	Heroin	Negative blood cultures × 16 autopsy Staph C P from liver abscess and IVC vegetations	No valvular involv	None	Fever & chills cough, chest pain 25 lbs wt loss	Methacillin Cephalothin Gentamicin	Died

Results of cultures of drugs

Although we found frequent contamination of street drugs on culturing neither cocaine nor brown or white heroin yielded a single colony of *Staphylococcus aureus* Neither did we isolate any strains of *Streptococcus viridans* candida or *Pseudomonas aeruginosa* The bacterium most often recovered from the drug specimens was *Bacillus subtilis* and the fungi found most frequently were aspergilli (see Table II)

Discussion

In May 1975 an editorial in the *New York Times* noted that on the basis of increasing numbers of arrests for heroin related felonies it had become apparent that increasing quantities of heroin were becoming available on the street market in both the regular white form of European origin and a newer brown form originating in Mexico [1] Brown heroin had first made its appearance in 1973 74 at a time when the ban

Table III "Street drug culture results

7 samples of cocaine	– Streptomyces B Subtilis × 2 Aspergillus sp Pleosporum sp
12 samples Brown Heroin	– Aspergillus sp × 3
12 samples White Heroin	– Pleosporum sp × 2 Streptomyces B Subtilis

on poppy growing in Turkey resulted in a significant decrease of the traditional supply Although less purified, the brown heroin was noted to be more potent It was felt that a "new heroin epidemic' was a serious and likely possibility in the near future

The marked increase in the number of cases with heroin associated endocarditis diagnosed in our hospital during this period corresponds closely to the above listed dates We observed a decrease in the number of cases in 1973 and 1974 (two definite for each year and one and three suspected respectively), followed by a steep rise in incidence in 1975 *

We wondered whether there might be a relationship between the increase in septic complications observed in our addict population and the more frequent use of brown heroin It was felt that the more unrefined impure heroin originating from Mexico was possibly more heavily contaminated with pathogens The results of our cultures of samples of cocaine, white and brown heroin did not, however, lend credence to this hypothesis Despite our finding of heavy contamination of street drug samples we failed to recover a single isolate of *Staphylococcus aureus* the pathogen responsible for 63 6 per cent of the infective endocarditis cases in 1975 We failed in addition to isolate any of the other organisms causing endocarditis in our addicts namely candida, pseudomonas or alpha streptococcus We were unfortunately unable to obtain the injection paraphernalia used by the couple suffering from *Streptococcus viridans* endocarditis

Others have also failed to recover offending organisms from the drugs and injection paraphernalia used by addicts Although the isolation of strains of pseudomonas and candida has occurred,[9, 16] only a single isolation of *Staphylococcus aureus* from heroin[17] has been made to date The drugs and paraphernalia[16] may not be the source of the offending organisms Tuazon and colleagues[18] reported that on culturing nose, skin, and throat of drug addicts 33 per cent were found to be carriers of *Staphylococcus aureus* as compared to only 11 per cent in controls Moreover, when studied within the first 3 days after initiating therapy for addiction associated staphylococcal endocarditis, 100 per cent of patients showed identical phage type staphylococci from nose, throat, or skin as grew from the initial blood cultures[18] Interestingly, these authors also found similar increases in staphylococcal carrier rate among diabetics on chronic insulin injection therapy[18]

Available present data, therefore, suggest that heroin injection increases staphylococcal carriage and that self inoculation during nonsterile injection of skin contaminating staphylococci accounts for frequent staphylococcal bacteremia and consequent endocarditis

Since the majority of our addicts had been using heroin for several years this hypothesis does not fully explain the marked increase in incidence in 1975 Heroin was used on a periodic rather than on a daily basis by many of our addicts If we assume that each intravenous injection carries a certain constant percentage risk it might follow that if increased availability of heroin on the street led to greater frequency of injections among the addicts a greater number of cases of staphylococcal sepsis and hence of endocarditis would occur It might also be that in some undefined manner the injection of brown heroin increases the carrier state of staphylococci even more than does white heroin

The criteria for establishing the diagnosis of tricuspid endocarditis remain somewhat controversial It is primarily a clinical diagnosis made on the basis of repeated positive blood cultures multiple pulmonary infiltrates, fever and a history of parenteral heroin use[9] Different series vary considerably in the proportion showing a typical tricuspid insufficiency murmur[2, 3, 6]

That the above listed criteria for diagnosing tricuspid endocarditis can be present without actual involvement of the tricuspid valve is shown by our patient No 20 This patient who

(11 definite and five suspected)

had an intermittent murmur multiple pulmonary emboli fever and a history of heroin abuse but whose blood cultures were consistently negative was found to have multiple staphylococcal liver abscesses that had eroded into the inferior vena cava Hence the infection was peripheral to the right side of the heart the tricuspid and pulmonary valves were found to be totally normal at autopsy despite continuing evidence of multiple sites of embolic pneumonia To our knowledge this case is unique

In order to establish the diagnosis of tricuspid endocarditis more clearly cardiac catheterization has been utilized to obtain blood for bacteriologic culture above and below the tricuspid valve thereby establishing the definite anatomic level at which infection is present [13, 8] The risk of embolization as a direct consequence of such catheterization however makes this a dangerous procedure that should be undertaken only in cases of persistent infection or unsatisfactory clinical response after a trial of appropriate medical therapy

Our series supports the increasingly frequent reports of a favorable outcome for right sided endocarditis caused by staphylococci when a high level of suspicion is maintained and appropriate antibiotic therapy is begun immediately after the diagnosis is seriously suspected [8] This is in marked contrast to the right sided endocarditis produced by pseudomonas infection a disease that continues to have a bleak prognosis Indeed in a local epidemic described by Arbulu and colleagues [1] and by Reyes and co workers [2] which occurred in Detroit a relatively favorable outcome was only achieved after surgical excision of the tricuspid valve Medical therapy for six weeks frequently resulted in relapse following discontinuation of the antibiotics Currently recommended medical therapy includes gentamicin carbenicillin and polymixin given together [2]

Left sided endocarditis caused by staphylococci on the other hand remains a disease with a serious prognosis if the aortic valve is involved The disease is particularly severe if the causative organisms are strains of candida or pseudomonas On the other hand if the left sided disease is caused by *Streptococcus viridans* treatment is usually successful

Of the eight patients with left sided endocarditis five had a history of previous rheumatic heart disease In one patient this had led to the insertion of a mitral valve prosthesis All three of our candida cases occurred in this group giving further support to the observation that candida usually colonizes previously damaged heart valves [3] Of the 13 patients with staphylococcal endocarditis nine occurred on the right side of the heart Of four patients with staphylococcal infections involving left sided cardiac valves two had a history of previous rheumatic heart disease In only two patients therefore did staphylococci colonize left sided cardiac valves presumed to be normal

It has been observed that platelets are aggregated in vitro by various bacteria and that large numbers of viable clumped bacteria can be found within the aggregated platelet mass [27, 28] Of the bacteria studied staphylococci showed the greatest promotion of aggregation [27, 2] It is unknown if there are specific factors that cause these platelet-staphylococcal aggregates to settle out predominantly on the right sided heart valves

The presumed transmission of *Streptococcus viridans* by shared paraphernalia has to our knowledge not been reported previously There is one instance in which enterococci caused endocarditis in both husband and wife using heroin [31] This is of particular interest in view of a recent paper[2] reporting isolation of enterococci from the paraphernalia of heroin addicts with enterococcal endocarditis The narcotic samples we studied unfortunately did not include the drugs used by the husband and wife with streptococcal endocarditis However it still seems likely the shared needles and drugs accounted for the conjugal aortic valve endocarditis

Conclusion

The reason for the sharp increase in the number of cases in 1975 in our series remains obscure We could not implicate the drugs and there was no evidence of a point source Several organisms were involved and phage typing of four of the seven 1975 cases of *Staphylococcus aureus* infection revealed at least three different phage types Since the drug samples were from addicts other than those who developed endocarditis and since we did not study the paraphernalia from the patients with endocarditis drug or paraphernalia contamination is *still* a possibility If however

there was no point source and drug contamination could not be demonstrated, an intriguing possibility is that the brown heroin modifies host defenses or microbial carriage rates more than white heroin

Summary

The total number of cases of heroin induced endocarditis occurring over a four year period were reviewed in order to explain an increase in the number of cases in the last year studied (1975) Brown heroin was noted to be used more frequently by addicts during the period of increased incidence Cultures of street samples' of brown and white heroin as well as cocaine were obtained in order to elucidate a possible relationship between the increased use of brown heroin and the increased number of endocarditis cases Despite frequent contamination of both white and brown heroin, none of the common endocarditis causing pathogens were isolated from the samples

Staphylococcus aureus, the most common etiological agent, frequently resulted in tricuspid endocarditis That the accepted criteria for tricuspid endocarditis may be present without actual cardiac valve involvement is demonstrated by a most unusual case of hepatic vasculature infection

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The temperature course in acute myocardial infarction

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Most patients with acute myocardial infarction (AMI) develop fever during the first days of their disease In earlier days when the temperature course was an important factor for diagnosing AMI several studies were performed where temperature was correlated to the clinical course[1,2,3] A more detailed analysis of the temperature course was performed by Eckerstrom[3] and by Forssman However in all these studies AMI was diagnosed mainly by clinical signs partly by electrocardiograms (ECG) but not by serum enzymes

The main reason for measuring the temperature in patients with AMI today is to diagnose complications For this purpose the normal temperature course must be known Most patients become afebrile in the beginning of the second week[3,5] However some patients run another temperature course and they present a difficult problem still only infarction fever or a complicating infection or an early post myocardial infarction syndrome (PMI syndrome)[7] Though exceptional with proper techniques the infection *may* be a septicemia as a consequence of different catheters used in the coronary care unit (CCU) and this possibility makes a correct diagnosis especially urgent Yet patients with prolonged infarction fever or early PMI syndrome should ideally not undergo an empirical treatment by high dose antibiotics With this background we studied a consecutive series of AMI patients retrospectively to find some guidelines for our handling of fever problems in AMI

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Recei ed f r publication J n 7 197

Accepted f r publication Oct 20 1977

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Materials and methods

The temperature recordings of 192 consecutive patients with AMI were studied * The patients had been admitted to the CCU because of prolonged chest pain frank pulmonary edema or syncope The diagnosis of AMI was based upon (1) appearance of a pathologic Q wave and/or appearance or disappearance of a localized ST elevation followed by a T inversion and/or (2) two raised SGOT (ASAT) values with a maximum about 24 hours after onset of symptoms in association with lower SGPT (ALAT) values, (3) findings at autopsy of myocardial necrosis of an age corresponding to the onset of symptoms

Seven patients died during the first two days and were excluded as their temperature recordings could not be further analyzed Another 25 patients (Table I) were excluded due to treatment with antibiotics during the first ten days because of a diagnosed or suspected infection Left for study were 160 patients of whom eight had two AMIs during the hospital stay Thus the study will include 160 patients with 168 AMIs

Results

Eighteen patients (11 per cent) did not have fever on any day of their hospital stay

As can be seen from Fig 1 only four patients (3 per cent) had a temperature above 38 2° C in the first hospital morning

In 145 of the 150 AMI cases with fever (97 per

*The temperature was measured rectally every morning in hospital and fever was defined as a morning temperature above 37 0 C

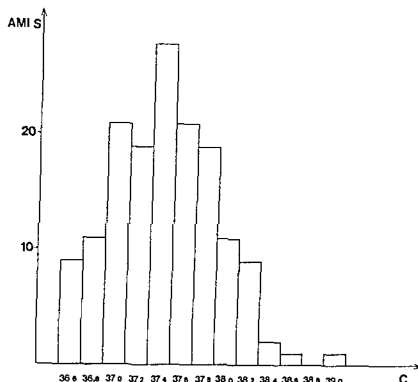


Fig 1 Temperature in the first morning in hospital One hundred fifty AMI cases with fever

Table I Patients (n = 25) primarily excluded due to treatment with antibiotics during the first ten days because of a diagnosed or suspected infection

Diagnosed or suspected cause of fever besides AMI	*No*	*Temperature course atypical for AMI* No*
Urinary tract infections	11	3
Upper respiratory infections	2	0
Pneumonias	3	3
Operation/wound infections	5	4
Septicemia(?) + pulmonary emboli	1	1
Tuberculosis (treatment)	1	1
Fever of unknown cause	2	1

Regarding Temperature course atypical for AMI see text

cent) the temperature reached its maximum on day 2 to 5 in hospital The remaining five patients had their maximal temperatures on day 6 9 9 14 and 20

Eight patients had two temperature maxima in all cases due to a reinfarction

Only one (1 per cent) of the patients with fever had a morning temperature above 39 0° C (Fig 2) during hospital stay

On the eighth day 43 patients (26 per cent) had fever (Fig 3) These patients had higher SGOT maxima than the rest of the series (259 ± 134 v 138 ± 77 I U/L, m ± SD $p < 0.001$) On the eleventh day 18 patients (11 per cent) still had fever All of these had had intravenous catheters during the CCU period, five of them had also had catheters in the aorta the heart or the bladder

For clinical reasons seven of the 18 patients had after the eleventh day, been given a tentative treatment with high dose antibiotics parenterally and eleven had not Only two of the seven treated patients responded with a normalized temperature in due time One of them was the only patient with a morning temperature above 39 0° C and his maximum occurred on day 20 In one of the five non responders antibiotics were discontinued and no other treatment started His temperature gradually fell to 37 0° C in 24 days in hospital After 14 days only seven patients (4 per cent) had fever (Fig 3)

From a maximum on day 2 to 5 the temperature generally fell gradually with minor oscillations In order to study this part of the curves the consecutive morning temperatures after day five were analyzed Generally the morning temperature was either lower or unchanged compared to the morning before In some patients however an increase in temperature occurred in some mornings after day five and the sum of these increases in each patient was analyzed In nine patients (6

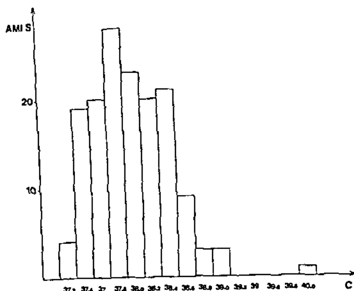


Fig 2 Maximal morning temperature recorded during hospital stay One hundred fifty AMI cases with fever

per cent) this sum exceeded 0 6 C Eight of these nine patients reached a second temperature maximum

These results indicate that the ordinary temperature course after AMI is characterized by (1) a temperature below 38 2 C in the first hospital morning (2) a morning temperature maximum occurring on day 2 to 5 in hospital (3) a maximal morning temperature below 39 0 C (4) if any temperature increase occurs from one morning to the next after day five the sum of these increases is not more than 0 6 C

Lastly the temperature recordings from the 25 patients excluded due to treatment with antibiotics (Table I) were compared to the findings above Thirteen of these patients (52 per cent) had a temperature course which would have been considered atypical for AMI The other twelve patients with ordinary AMI fever generally had urinary or upper respiratory tract infections as the cause of antibiotic treatment

Discussion

Naturally it is impossible to present a normal AMI temperature course and conclude that all other courses indicate a complication The aim of the present investigation was to find some guidelines for the practical handling of fever in AMI

The results indicate that a concomitant cause of fever besides the AMI should at least be considered if the temperature (1) is above 38 2° C in the first hospital morning (2) if it reaches its maximum before day two or after day five (3) if it reaches a maximum above 39 0° C and/or (4) if it increases more than 0 6° C after day five in one or more steps

These findings are partly in accordance with those of earlier series Forssman[4] found that the temperature is generally not elevated during the first 12 hours after onset of symptoms and the maximal temperature is generally reached on day 2 to 5[1,5] Maximal morning temperature seldom exceeds 39 0 C[3] Worth noting is that all patients with AMI do not have fever In Eckerstrom s series[3] 20 per cent of the patients did not have fever and the corresponding figure in this series was eleven per cent This difference is probably due to different diagnostic criterias

In Eckerstrom s series[3] 55 per cent of the patients were afebrile after one week and 94 per cent after two weeks The corresponding figures in the present series were 74 per cent and 96 per cent

Forssman[4] found a correlation between the duration of fever and the maximal temperature and a tendency towards this was seen also in this study

Patients with fever for more than one week had higher SGOT maxima than the rest of the series which corresponds to Woodhead s finding of an association between peak SGOT and the area

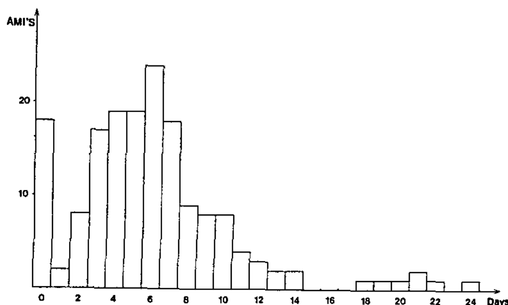


Fig 3 Duration of fever after AMI in all 168 cases

below the temperature curve, but not with maximal oral temperature

According to Kossowsky and associates[6] fever of long duration could indicate an early PMI syndrome The 11 patients in this study with fever for more than ten days and who were not treated with antibiotics were further examined with history, cardiac physical examination sedimentation rate, and chest x ray but in no case did the examinations support a diagnosis of an early PMI syndrome

Conclusions

A concomitant cause of fever besides the AMI should at least be considered if the temperature (1) is above 38 2° C in the first hospital morning (2) if it reaches its maximum before day two or after day five (3) if it reaches a maximum above 39 0° C and/or (4) if it increases more than 0 6° C after day five in one or more steps

Summary

The rectal temperature course was studied retrospectively in 192 consecutive patients with acute myocardial infarction (AMI) The ordinary temperature course after AMI was characterized by four points

1 The morning temperature on the first day in hosptial was seldom above 38 2° C (in four of 150 cases)

2 The maximal morning temperature was seldom recorded before day two or after day five in hospital (in five of 150 cases)

3 The maximal morning temperature seldom reached above 39 0° C (in one of 150 cases)

4 The morning temperature seldom increased more than 0 6° C after day five in one or more steps (in nine of 150 cases)

Seventy four per cent of the patients were afebrile after one week, and 96 per cent after two weeks Patients with higher SGOT (ASAT) maxima had longer duration of fever Eleven per cent of the patients did not have fever at all

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Systolic flutter of the mitral valve

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Diastolic flutter of the mitral valve is a well recognized echocardiographic finding frequently observed with aortic incompetence In contrast systolic flutter of the mitral valve is distinctly uncommon and has received little attention This report presents 11 cases of systolic flutter of the mitral valve which were identified from approximately 6 000 studies in our laboratory during the past 3 ½ years The echocardiographic features are correlated with the clinical presentation and in six cases with available pathological specimens The association of systolic flutter of the mitral valve with the *presence of* mitral regurgitation and coexistent bacterial endocarditis is emphasized Our findings differ from a previous report which suggested association of systolic flutter with ruptured chordae tendineae and apparently did not evaluate as a causative factor the role of bacterial endocarditis which had occurred in some of their patients

Materials and Methods

Echocardiographic records were examined for all patients indexed with the finding of *systolic flutter of the* mitral valve Eleven previously identified cases out of approximately 6 000 studies performed in the past 3 ½ years were confirmed by two independent reviewers Hospital records were reviewed in these 11 cases

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Supported in part by contract HL 05500 From th N tional He rt and Lu g Inst t t N t n l Inst t tes f Health Bethesd Md.

Rece ed f r p blic t on J 14 1977

Accepted f r publ tion Aug 31 1977

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The results of the above study prompted us to examine 59 other patients with mitral regurgitation studied in the same period All of them had adequate echocardiographic studies and confirmation of mitral valve lesions by surgery and/or pathology The valvular lesions consisted of papillary muscle dysfunction (four cases) and papillary muscle rupture (three cases) due to ischemic heart disease bacterial endocarditis involving the mitral valve (four cases) mitral valve prolapse with associated idiopathic chordae tendineae rupture (10 cases) severe mitral valve prolapse with elongated but intact chordae tendineae (seven cases) isolated rheumatic mitral regurgitation (eight cases) and rheumatic mitral regurgitation with associated stenosis (23 cases) In addition 70 cases of angiographically proven mitral regurgitation and 50 recent cases of clinically diagnosed mitral regurgitation were also reviewed

All echocardiographic examinations were performed using a Picker echograph and a 2 0 or 2 25 MHz collimated transducer Continuous records were made on 35 mm film at an effective speed of 125 mm /sec by means of a Fairchild oscilloscope record camera and a dual beam oscilloscope acting as a slave Echocardiographic recordings of the cardiac valves and chambers were obtained by standard methods Mitral valve echoes were also recorded at 2× magnification in some cases demonstrating systolic flutter Additional high speed recordings at 375 mm /sec were performed to clarify subtle flutter of the mitral valve

Mitral valve echocardiograms were examined for amplitude frequency and predominant location of the systolic flutter evidence of mitral valve prolapse flail mitral leaflet(s) rheumatic mitral valve disease and shaggy thickened

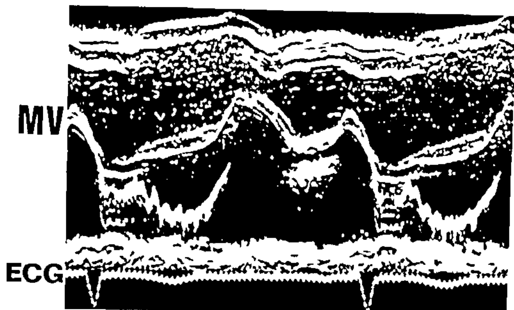


Fig 1 Systolic flutter of the mitral valve in a patient with mitral valve prolapse and healed bacterial endocarditis (Case 5) The flutter is seen predominantly on the prolapsing mitral segment and has a frequency of 40 Hz in this record

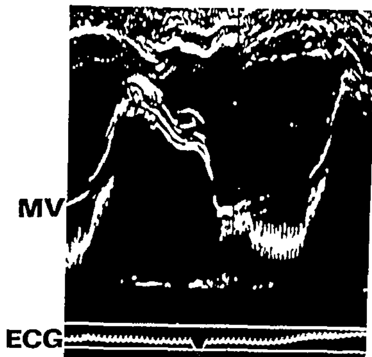


Fig 2 Mitral valve echocardiogram demonstrating larger amplitude higher frequency (80 Hz) systolic flutter This record is from the same patient as *Fig 1*

echoes suggestive of bacterial vegetations Measurements of the systolic flutter were averaged over four cardiac cycles

Mitral valve prolapse was diagnosed if records demonstrated a distinct steplike posterior motion of the mitral leaflet in midsystole or holosystolic sagging of at least 3 mm posterior to the mitral C point [5,6]

A flail mitral leaflet was diagnosed by erratic, bizarre undulations of either leaflet in diastole paradoxical anterior motion of a portion of the posterior mitral leaflet in diastole, or linear structural echoes from the mitral leaflets detected in the left atrial cavity behind the aortic root [3,7,9]

Results

All eleven patients with systolic flutter of the mitral valve (nine males and two females aged 46 to 74 years) had murmurs of mitral regurgitation None had a clear history of antecedent acute rheumatic fever Based upon echocardiographic findings, mitral valve prolapse was present in 10 cases and flail mitral leaflet(s) in seven cases (Table I) Mitral regurgitation was demonstrated in each of the seven patients who underwent left ventricular angiography In all 11 patients the systolic flutter of the mitral valve was of high frequency, ranging from 30 to 100 Hz with a mean of 66 Hz The maximum amplitude of the flutter varied from 2 to 6 mm with a mean of 4 5 mm In six patients the systolic flutter was predominantly recorded on the prolapsing portion of the mitral leaflet Figs 1 and 2 illustrate typical examples of the systolic flutter In two patients *with flail mitral leaflets the flutter was prominently* seen in mitral segments echoed in the left atrium behind the aortic root (Fig 3) The high frequency flutter was superimposed on a coarser undulating movement of the valve in these two patients Echoes from the usual mitral valve recording position failed to show systolic flutter in one of these two patients Undulating movements of this type (< 25 Hz) were not seen in any other patients in this group

Nine of the 11 cases had prior or concurrent

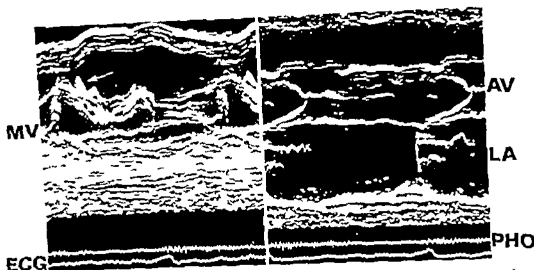


Fig. 3. *Left*, Mitral valve echocardiogram from Case 2. There are shaggy echoes and coarse diastolic undulations *(arrow)* consistent with bacterial vegetations and *chordae rupture*. Systolic flutter is not seen. Other records showed classical mitral valve prolapse. *Right*, Aortic root echocardiogram. Coarse and fine flutter of prolapsing mitral elements are recorded in systole *within the left atrial cavity*. These findings were absent prior to bacterial endocarditis.

Table I. Findings in patients with systolic flutter

Patient	Clinical SBE	Echo: Systolic flutter: Frequency (Mean) (Hz)	Echo: Systolic flutter: Amplitude (Max) (mm.)	Echo: MVP	Echo: Flail leaflet	Surgical/Pathological: Chordae rupture	Surgical/Pathological: SBE	Surgical/Pathological: Myxoid degeneration	Surgical/Pathological: Other
1. M L	+	80	5	S	+	+	+	+	Billowing leaflets. Cleft posterior leaflet. Moderate aortic insufficiency
2. W S	+	60	5	S	+	+	+	+	Billowing leaflets
3. I S	+	100	6	S	0				Not available
4. A H	+	80	3	S	0				Not available
5. W H	+	70	5	S	0				Not available
6. N F	+	80	3	H	+	+	+	+	Partial fusion to ventricular wall
7. I S K	+	40	3	S	0	0	0	+	Billowing thin posterior leaflet
8. J O	+	80	5	S	+	0	+	+	
9. C R	+	30	4	0	+				Not available
10. J B	0	80	6	S H	+	Flail billowing posterior leaflet confirmed by angiography			
11. S D	0	30	5	S	+	+	0	+	Elongated chordae, billowing posterior leaflet

Abbreviations: + = present; 0 = absent; H = holosystolic sagging; Max = maximal; MVP = predominant mitral valve prolapse pattern; S = steplike displacement in midsystole; SBE = subacute bacterial endocarditis.

bacterial endocarditis at the time of echocardiographic study documented by multiple positive blood cultures in an appropriate clinical setting including fever, heart murmur of mitral regurgitation, and no other apparent source for the sustained bacteremia. The infecting organism was an alpha streptococcus in eight patients and *Staphylococcus aureus* in the remaining patient (Case 9). Two patients (Cases 6 and 8) had two episodes of alpha streptococcal endocarditis. Echocardiograms showed shaggy thickening of the mitral valve highly suggestive of bacterial vegetations in two patients. Multilayering with some thickening was observed in four patients, while no evidence for bacterial endocarditis was present in the remaining three patients.

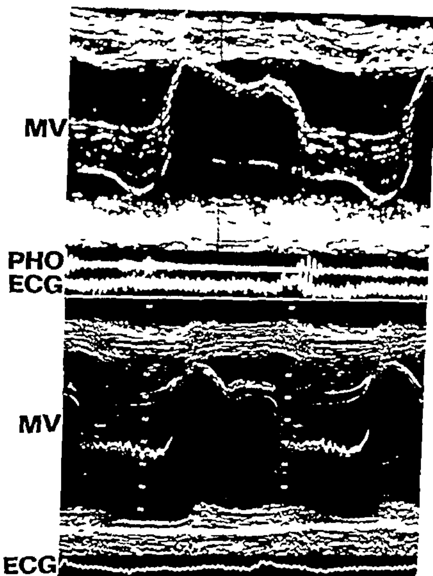


Fig 4 *Upper panel* Mitral valve echocardiogram prior to bacterial endocarditis (Case 1) Note the typical prolapse pattern and absence of systolic flutter *Lower panel* Mitral valve echocardiogram following bacterial endocarditis Note the development of high frequency systolic flutter Other records obtained with higher gain settings demonstrated shaggy thickening and diastolic instability highly suggestive of bacterial endocarditis with chordae rupture

In two patients with auscultatory evidence of mitral valve prolapse echocardiograms obtained prior to the development of bacterial endocarditis showed no evidence of mitral systolic flutter One of them demonstrated typical mitral valve prolapse (Fig 4 *upper*), while the other showed some posterior displacement in systole, but was not definitive for valve prolapse Subsequent echocardiograms during and following treatment for bacterial endocarditis showed development of systolic flutter as well as shaggy thickening of the mitral leaflets which appeared to be flail (Figs 3 and 4, *lower*) A typical mitral valve prolapse pattern became evident in the second patient

Pathological findings were available in five of nine patients with bacterial endocarditis (Table I) In all five patients the mitral leaflets were reported to be flexible and generally redundant Although large vegetations were not present in any patient the histological findings showed areas of fibrosis and vascularization consistent with healed bacterial endocarditis in four and myxoid degeneration in all Interestingly, in the patient without obvious evidence of scarring it was difficult to find the systolic flutter which was localized to a small portion of the mitral systolic segment Pathological findings were unavailable in three patients who remained asymptomatic following cure of their endocarditis Two patients had systolic flutter of the mitral valve without any history of bacterial endocarditis In one patient the flutter was limited to a few vibrations in early systole and was difficult to locate Both patients had severe mitral valve prolapse with flail posterior leaflets demonstrated by echocardiography and confirmed by angiography In one

patient pathological examination showed very thin mitral leaflets with elongated and ruptured chordae tendineae There was advanced myxoid degeneration with no evidence for bacterial endo carditis

Systolic flutter of the mitral valve was not noted in any of 179 other patients with mitral regurgitation studied in the same period These included four patients with bacterial endocarditis involving the mitral valve Mitral regurgitation was judged to be mild or minimal in two instances

Discussion

Our study indicates that systolic flutter of the mitral valve is relatively rare and is always associated with an abnormal mitral valve All patients with this finding had mitral regurgita tion due to mitral valve prolapse or chordae rupture and all but two had associated bacterial endocarditis The regurgitant jet of blood across the edge of the incompetent mitral leaflet(s) during systole apparently generates the vibra tions recorded by echocardiography This is supported by the fact that the systolic flutter was most prominently recorded from the prolapsing or flail portion of the mitral valve in over half the instances In addition to the regurgitant blood flow the characteristics of the mitral leaflets are also important for the development of flutter Pathology has shown scarring superimposed on flexible redundant mitral leaflets in cases where the systolic flutter has been easily recorded The flexibility allows motion of the leaflets to occur whereas the stiffness imparted by the scarring process apparently enables the thickened struc ture to vibrate rapidly in the presence of turbu lence resulting from the high velocity regurgitant jet In addition the thickened leaflet is a strong reflector of ultrasound thereby making recording of the phenomenon more likely In the two patients where pathology demonstrated very thin ballooning mitral leaflets without any scar ring the flutter was difficult to locate limited to a small portion of the mitral systolic segment and was noted to have a somewhat lower frequency

The genesis of systolic flutter of the tricuspid valve has also been attributed to a similar mech anism It has been reported in patients with congenital left ventricular-right atrial communi cation and is probably due to the passage of a left ventricular jet of blood into the right atrium through a deformed and thickened tricuspid valve [1] It does not occur when the shunt is above the valve level or in tricuspid insufficiency

Marked thickening rigidity and calcification of the mitral leaflets would be expected to restrict systolic flutter We have not observed systolic flutter of the mitral valve in any of our patients with echocardiogrphic features of rheumatic mitral valve disease In the literature, a patient with mitral stenosis and only a slightly thickened valve demonstrated systolic flutter following closed mitral commissurotomy complicated by possible chordae rupture [2] The setting of a new regurgitant jet across a somewhat thickened but apparently flexible valve is consistent with our postulation of the requirements necessary for the development of systolic flutter

Based upon a small number of cases Meyer and colleagues considered systolic flutter to be a specific and not uncommon finding for ruptured chordae tendineae However our findings demon strate rupture of the chordae tendineae is not necessary for the causation of high frequency systolic flutter Two of our patients with systolic flutter had intact chordae tendineae demon strated at surgery Three additional patients with systolic flutter lacked echocardiographic evidence of a flail mitral leaflet were asymptomatic following cure of their endocarditis and were considered unlikely to have had chordae rupture although definitive proof is lacking Furthermore systolic flutter is uncommon (13 per cent) in patients with ruptured chordae tendineae or papillary muscles in the absence of bacterial endocarditis Interestingly three of four patients reported by Meyer and associates[2] who under went surgery had prior bacterial endocarditis

When endocarditis is suspected detection of flutter may serve as a clue to its location since other diagnostic features of a vegetation may be absent or in some instances difficult to distin guish from multilayered echoes of mitral valve prolapse It should be emphasized that high speed recording (125 mm /sec) and image magni fication may be needed for delineating subtle flutter

Summary

Systolic flutter of the mitral valve was observed in 11 cases during the past 3 1/2 years All patients had mitral regurgitation due to mitral valve prolapse or flail leaflets and nine of the 11 (82 per cent) had prior or concurrent bacterial

endocarditis Systolic flutter is uncommon in the absence of endocarditis and was observed in only two of 15 patients (13 per cent) with proven chordae tendineae or papillary muscle rupture without historical and pathological evidence of infection involving the mitral valve Systolic flutter was also not seen in a large number of patients with mitral regurgitation due to other causes It is postulated that the regurgitant jet of blood across the edge of a structurally abnormal but flexible mitral leaflet is important for the development of flutter

We are thankful to Dr Paul Yu for reviewing this manuscript and to Mrs Beth Nestorowycz for her secretarial help

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The management of anticoagulation during noncardiac operations in patients with prosthetic heart valves

A Prospective Study

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In a previous study of thromboembolism and hemorrhage among patients with prosthetic heart valves undergoing noncardiac operations there was significant peri operative bleeding when anti coagulation was maintained during such operations Also among patients with mitral valve prostheses there was significant peri operative thromboembolism when anticoagulation was dis continued

The need for some means of managing patients with thrombogenic caged ball or caged disc cardiac valves who require subsequent noncar diac operations was the impetus for this prospec tive study of 45 operative procedures performed among a group of 235 patients on chronic antico agulation with prosthetic valves † Because in the earlier study there had been no adverse effect from the interruption of anticoagulants for three to five days among patients with only aortic valve prostheses simple interruption was employed in the present study for such patients For patients with mitral caged disc prostheses either alone or in combination with an aortic or tricuspid pros thesis restoration of anticoagulation with heparin was used in the early postoperative period to prevent thromboembolism

Methods

The following protocol for the management of anticoagulation during noncardiac operations was used For patients with isolated aortic valve prostheses warfarin was discontinued in time to produce a normal prothrombin time on the day of operation and oral anticoagulation was resumed two days after operation (One patient with an aortic valve prosthesis also received heparin early after operation because of a presumed increased risk of thromboembolism) Patients with mitral or combined prostheses underwent rapid reversal of their warfarin effect with parenteral vitamin K during the 24 hours before operation and received intravenous heparin beginning 12 hours after operation Heparin anticoagulation was main tained by either intermittent or continuous intra venous infusion to produce a partial thrombo plastin time of one and one half to two and one half times the levels of normal controls When adequate surgical hemostasis was assured usual ly three days after operation oral anticoagulation with warfarin was resumed and the heparin was stopped when the prothrombin time reached a therapeutic level

A noncardiac operation was classified as major if a body cavity or bone was entered and otherwise as minor There were 23 major oper ations which included hysterectomy (eight) pulse generator change (five) bowel resection

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Rece ed f publi ti n J e 16 19

A epted fo publicat n Aug 31 1977

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Table I Thromboembolism or hemorrhage in patients with prosthetic valves during subsequent noncardiac operations

Patient group	*Aortic valve only*	*Mitral & combined valves*
Number	18	21
Operations		
Major	10	13
Minor	9*	13
Total	19	26
Management	Stop warfarin	Stop warfarin add heparin
Thromboembolism	0	0
Hemorrhage	1†	2

Two dental extractions were performed with anticoagulation maintained

†This patient received heparin early after operation

(four), cholecystectomy (three), subtotal gastrectomy (two), and craniotomy (one) There were 22 minor operations which included biopsy or excision (nine), dental extraction (five), arteriography (four) mastectomy (two) and hemorrhoidectomy (two)

Results

Thirty nine patients have undergone 45 noncardiac operations under this protocol Table I summarizes the experience in terms of peri operative thromboembolism and hemorrhage There were no deaths Thromboembolism did not occur among the patients with isolated aortic valve prostheses despite the discontinuation of anticoagulation for three to five days There was an incisional hematoma which occurred in a patient who received heparin early after operation because of an increased risk of thromboembolism In this case the bleeding was minor and easily controlled Dental extractions were performed on two patients with prosthetic aortic valves without the cessation of anticoagulation and there were no complications Both had chronic atrial fibrillation and were the only patients in the aortic group with this arrhythmia

When heparin was administered to patients with mitral or combined prosthetic valves early after operation no thromboemboli occurred Sixteen of these 21 patients (76 per cent) had chronic atrial fibrillation One patient developed an abdominal incisional hematoma but did not require transfusion or discontinuation of anticoagulant therapy One patient developed vaginal cuff bleeding after a vaginal hysterectomy and required transfusion, ligation of the bleeding site and brief interruption of heparin

Discussion

The major problem for patients with mitral caged ball or caged disc prostheses undergoing noncardiac operations has been thromboembolism when anticoagulants are discontinued Under these circumstances the risk is increased when there is atrial fibrillation[1]

Others have reported that a hypercoagulable state is not associated with the interruption of warfarin therapy[3] The absence of thromboembolism during the short term withdrawal of warfarin from patients with aortic prostheses in this and our previous study[1] supports that observation However, it has also been observed that minor procedures performed in accessible areas such as dental extractions, can be safely accomplished with maintenance of warfarin[4] Our experience with the continuation of anticoagulation during dental procedures has also been favorable

In this study heparin was administered to patients with mitral prostheses in the early post operative period in order to avoid the previously observed problem of thromboembolism The advantage of heparin when compared to warfarin is the rapid reversal of its anticoagulant effect by protamine sulfate if major bleeding should occur The result from the use of heparin in these patients was the avoidance of thromboemboli, however, hemorrhage did occur in three patients This incidence of hemorrhage (10 per cent) in our patients is similar to a previous report[5] in which anticoagulation was started soon after an operative procedure Since these bleeding episodes occurred when the partial thromboplastin time was in the appropriate therapeutic range[6] future consideration might be given to the use of lower doses of heparin It is probable also that the increasing use of non thrombogenic mitral xenografts will minimize this difficult management problem in the future

Summary

Based on previous thromboembolic complications associated with the interruption of anticoagulation during subsequent noncardiac operations in patients with nonbiological mitral prostheses a protocol was developed for this high risk

group We report the successful management of 26 such operations in which anticoagulation was interrupted for 12 hours and then rapidly restored by means of heparin in the postoperative period Since an earlier study suggested no adverse effect from the interruption of chronic anticoagulants for three to five days among patients with isolated aortic valve prostheses simple interruption was again employed during 16 subsequent noncardiac operative procedures in this group with no complications There were three episodes of hemorrhage observed in patients receiving therapeutic doses of heparin postoperatively but only one required blood replacement

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Organized left atrial mural thrombus demonstrated by coronary angiography

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A variety of uncommon cardiovascular abnormalities have been demonstrated by coronary angiography, including cardiac tumors,[1-3] vascular malformations,[4] and coronary arterial fistulas[5-13] This communication describes an angiographic abnormality which has a characteristic appearance, was observed during selective coronary angiography in three patients with mitral stenosis, and was due to organized mural thrombus that was adherent to the wall of the left atrial appendage

Clinical features of the patients

Table I summarizes the clinical features of the three patients with mitral stenosis in whom an organized left atrial mural thrombus was demonstrated by selective coronary arteriography The patients ranged in age from 67 to 75 years and had typical symptoms and findings of mitral stenosis on cardiac examination There was no history of a thromboembolic event in any of the three patients Patients No 1 and 3 had atrial fibrillation Chest radiographs demonstrated multichambered cardiac enlargement in each patient and mitral valvular calcification in patients No 1 and 2 Echocardiographic studies were made in patients No 1 and 2 and revealed findings typical of mitral stenosis but no evidence of intra atrial thrombi At cardiac catheterization the mean diastolic pressure gradient across the mitral valve ranged from 5 to 15 mm Hg and the area of the mitral valve orifice ranged from 0 6 to 0 9 square centimeters

Coronary angiographic findings

Selective coronary angiograms of these elderly patients were obtained prior to replacement of the mitral valve to exclude the possibility that their valvular disease might be complicated by coronary artery disease Coronary arteriography did not demonstrate coronary arterial luminal narrowing in any of the three patients However one (patient No 2) or two (patients No 1 and 3) small arteries, approximately 1 mm in diameter, were observed to arise from the circumflex coronary artery, course superiorly and terminate in a collection of radiographic contrast medium in the left atrial appendage (Fig 1, *A C*) The collections of radiographic contrast medium were small in patient No 2 and large in patients No 1 and 3 These collections were inhomogeneous in density and had irregular shapes and borders The contrast material appeared to flow from these collections into the lumen of the left atrium in the region of the appendage Because of the features just described these vascular channels were considered to represent small coronary arterial-left atrial fistulas

Anatomic findings

At operation a single thrombus was found within the left atrial appendage of each patient These thrombi ranged from less than 1 cm to 5 cm in length and were adherent to the wall of the left atrial appendage In each patient the thrombus was removed and the mitral valve was replaced Microscopic examination of the atrial

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Received for publication June 16 1977
Accepted for publication June 30 1977

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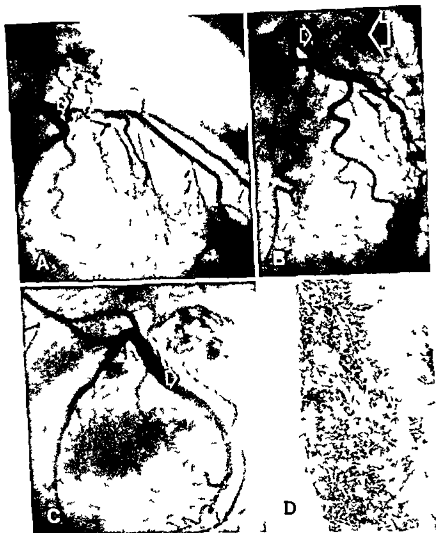


Fig 1 A through D *A C* Selective left coronary artery angiograms demonstrating coronary artery fistulas which terminate in a large or small collection of radiographic contrast medium in the left atrial appendage *A* Patient No 3 right anterior oblique view two atrial coronary artery fistulas (*arrows*) *B* Patient No 2, left anterior oblique view one atrial coronary artery fistula (*small arrow*) the collection of radiographic contrast medium is small (*large arrow*) *C* Patient No 1 left anterior oblique view two atrial coronary artery fistulas (*arrows*) *D* Histologic section showing organizing thrombus that was removed from the left atrial appendage of patient No 2 (Hematoxylin-eosin stain original magnification ×6 3)

thrombi showed various stages of organization (Fig 1D) The organizing areas of the thrombi had sinuses which contained red blood cells and the organized areas of the thrombi were dense with fibrous tissue Arterioles or venules were not present within the thrombus but a few small vascular channels were observed that were composed only of a single layer of endothelial cells There was no correlation between the size of the thrombus (Table I) and the size of the collection of radiographic contrast material observed during coronary angiography (Fig 1 *A C*)

Discussion

Non atherosclerotic cardiovascular abnormalities that are demonstrated by coronary angiography such as cardiac tumors vascular malformations and large coronary artery fistulas are uncommon but frequently have characteristic angiographic appearances These features differ from those observed in this study

To our knowledge arteriographic abnormalities due to cardiac tumors have been reported only in three cases a myxoma[1] a hamartoma[2] and a hemangioma A small amount of radiographic contrast material was observed in a left

Table 1 Patients with organized left atrial mural thrombus demonstrated by selective coronary angiography

Patient No	Age/sex	Cardiac symptoms	Murmurs	ECG	Chest radiograph	Echocardiogram	Mitral valve gradient (mm Hg)/ orifice (cm²)	Length of thrombus
1	67M	DOE and palpitations	MS MR	AF LAD	IPE RVE LAE LVE MV Ca	LAE MS	15/0 6	5 cm
2	69F	DOE PND palpitations	MS MR	1° AV block PVCs LAE	PVH RVE LAE MV Ca	LAE MS	18/0 6	5 cm
3	75F	DOE orthopnea palpitations	MS MR TR	AF IRBBB	PVH RVE LAE LVE	—	5/0 9	< 1 cm

Abbreviations and symbols —= data not available AF = atrial fibrillation AV = atrioventricular DOE = dyspnea on exertion ECG = electrocardiogram IPE = interstitial pulmonary edema IRBBB = incomplete right bundle branch block LAD = left axis deviation LAE = left atrial enlargement LVE = left ventricular enlargement MR = mitral regurgitation MS = mitral stenosis MV Ca = mitral valve calcification PND = paroxysmal nocturnal dyspnea PVCs = premature ventricular contractions PVH = pulmonary venous hypertension RVE = right ventricular enlargement TR = tricuspid regurgitation

atrial myxoma, presumably within the tumor, during selective right coronary angiography[1] A hamartoma[2] and a hemangioma[3] have been demonstrated in children by ascending thoracic aortography Both of these tumors were located at the apex of the heart Both tumors were supplied by enlarged, tortuous branches of the left anterior descending coronary artery these branches terminated in a dense mass of vessels that emptied slowly into the coronary venous system but did not communicate directly with the left ventricular chamber

Among coronary vascular malformations drainage of all left coronary arterial flow into the left ventricle through thebesian veins[4] has been recognized by means of coronary angiography Coronary angiograms demonstrated multiple, tortuous epicardial arteries terminating in an intense myocardial collection of contrast material which drained directly into the left ventricular chamber without filling any coronary veins or the coronary sinus

Large coronary arterial fistulas may be composed of a single vessel or many vessels and may involve one or more coronary arteries[5-13] Coronary arterial fistulas communicate with the right heart more often than with the left heart or with the pulmonary circulation[5-8] The small coronary-left atrial fistulas observed in this study appeared to empty directly into the left atrium without having demonstrable venous drainage These fistulas were small and could not have produced congestive heart failure or myocardial ischemia due to shunting of blood from the coronary arteries to the left atrium

An angiographic abnormality similar to the one which we have observed has been demonstrated at operation to be due to a ventricular[14] and to an atrial[15] mural thrombus The small vessels that we observed in the excised portions of the atrial thrombi were too small to account for the collections of radiographic contrast material that were observed during coronary angiography Therefore, we presume that these collections were present within vascular channels located either in the most basal portions of the thrombi or in the immediately subjacent areas of the left atrium Microscopic studies have demonstrated that cardiac mural thrombi may be invaded by new vessels as they become organized[16,17] Thus, it is possible that these ingrowing vessels form dilated vascular channels in an effort to resorb the thrombus

The following conclusions can be drawn from the data reviewed above (1) small arterial fistulas that terminate at the site of an adherent organized mural thrombus in the left atrial appendage may be observed incidentally during selective coronary angiography in patients with mitral stenosis (2) the angiographic features of this vascular abnormality can be distinguished from those of cardiac tumors vascular malformations and coronary artery fistulas that are not associated with organized thrombus (3) the vascular abnormality demonstrated by coronary angiography may be the only indication of the

presence of a left atrial thrombus (4) this abnormality may be present in thrombi that are not revealed by echocardiography and are not manifest clinically by systemic emboli and (5) the size of the collection of radiographic contrast material in the left atrial appendage is not proportional to the size of the thrombus

Summary

Small coronary artery fistulas terminating at the site of adherent organized mural thrombi in the left atrial appendage were observed during selective coronary angiography in patients with mitral stenosis The angiographic features of this abnormality can be distinguished from those of cardiac tumors vascular malformations and coronary artery fistulas that are not associated with organized thrombus This coronary angiographic abnormality may indicate the presence of left atrial thrombus that is not revealed by echocardiography and is not manifest clinically by systemic emboli The size of the collection of radiographic contrast material in the left atrium is not proportional to the size of the thrombus

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Idiopathic familial myocardiopathy in three generations A clinical and pathologic study

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Hypertrophic or non dilated cardiomyopathy frequently has a familial incidence[1-6] and demonstrates an autosomal dominant mode of inheritance In contrast in congestive or dilated cardiomyopathy it is rare to find families in which more than one member is affected [-9] and virtually all cases of congestive cardiomyopathy are considered sporadic This report describes clinical and morphologic features of an idiopathic non hypertrophic myocardiopathy which differs from sporadic idiopathic congestive cardiomyopathy both by its clinical presentation and its occurrence in three and possibly five generations of a single family (Table I) The autosomal dominant pattern of inheritance for the cardiac abnormalities in this family and the lack of distinctive structural abnormalities in the hearts of the three direct line descendents which were studied at autopsy suggest the possibility of a genetic metabolic abnormality of myocardium as a causative factor in this family and in some sporadic cases of idiopathic myocardiopathy

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Supported by Grant P50 HL 17655 02 from The National Institutes of Health Public Health Service Department of Health Education and Welfare and the Stetler Research Fund for Women Physicians

Received for publication *June 20 1977*

Accepted for publication July 30 1977

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Case report

On March 29 1973 approximately one year after the unexpected death of her son a previously healthy 44 year old *mother of three collapsed suddenly while playing tennis* She was brought into a local hospital in ventricular fibrillation was converted to sinus rhythm by electroshock but died four days later having not regained consciousness She was known to have had a systolic murmur since childhood first evaluated when she was three years old and believed to be functional Because of vague chest pain an evaluation 10 years before her death revealed a systolic murmur in the pulmonic area a normal sized heart and borderline abnormalities of the ST segment on electrocardiogram (ECG) One year before her death an ECG during exercise showed nonspecific ST segment abnormalities and premature ventricular contractions Although she denied any symptoms other than occasional chest pain over the eight year period before her death she had had two unexplained fainting spells

At autopsy her heart weighed 385 grams had a globular configuration mild acute fibrinous pericarditis and left ventricular dilatation and hypertrophy There was no disproportionate septal hypertrophy The mitral valve showed thickening and rolling of its margins (Fig 1) with chordal shortening but no commissural fusion The left ventricular endocardium was involved by a diffuse endocardial fibroelastosis (Fig 2) *Histologic examination of myocardium showed* scattered fibrosis prominent perinuclear lipofuchsin accumulation in muscle cells Basophilic degeneration present in moderate degree was evident by light microscopy which by

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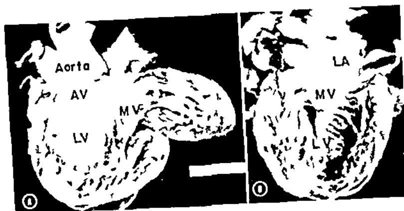


Fig 1 Views of left side of the heart of the index case (No 4) showing the globular configuration of the left ventricle endocardial fibroelastosis especially prominent in the left ventricular *(LV)* outflow area and rolling of the margins of the mitral valve leaflets secondary to mitral regurgitation *A* Outflow tract of left ventricle *AV* = aortic valve *B* Opened left atrium *(LA)* and left ventricle

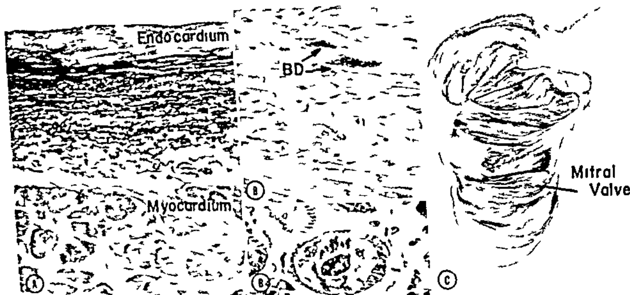


Fig 2 Histologic sections from heart shown in *Fig 1 A* Marked endocardial fibroelastosis The endocardium is approximately five times thicker than normal and contains prominent elastic lamellae stained black (Verhoff van Gieson stain original magnification ×375) *B* Myocardium showing strongly PAS positive intracellular material characteristic of basophilic degeneration *(BD)* (Periodic Acid Schiff stain original magnification ×125) *B lower panel* Transverse section of myocardial cell with basophilic degeneration (Toluidine blue stain original magnification ×750) *C* The rolled margin of the mitral valve showing changes characteristic of long standing mitral regurgitation (Verhoff van Gieson stain original magnification ×25)

ultrastructural examination consisted of circumscribed fibrillar deposits within the central portion of the myocardial cells No other abnormalities could be seen within myocardial fibers with or without basophilic degeneration and serial section studies of the atrioventricular conducting system showed no abnormality of the specialized conduction tissues The extramural and intramural coronary arteries were normal. Other organs and tissues showed no abnormalities. Death was attributed to ventricular fibrillation arising in a heart with mitral insufficiency and left ventricular dilatation hypertrophy and endocardial fibroelastosis of unknown etiology

Methods

Medical genealogical study The sudden unexpected death of this 44 year old woman approximately one year after the sudden death of her previously healthy 20 year old son suggested that a heritable cardiac disorder might exist within some segment of this family To explore this hypothesis a detailed family tree was constructed and medical information was sought

Table I Clinical data in five generations

	Patient number age & sex	Clinical history	Precordial murmur	Chest x ray	Electrocardiogram			Echocardiogram	Clinical course
					Short PR (< 12)	PVC	ST segment abnormalities		
Generation I	1 52F	Active unrestricted life	+	?	?	?	?	–	Sudden death due to fatty degeneration of the heart
Generation II	2 57F	Occasional heart attacks because of heart of someone who drank too much coffee over 2 years PTD otherwise well	+	?	?	?	?	–	Sudden death due to acute cardiac dilatation
Generation III	3 60F	Wolff Parkinson White syndrome active unrestricted life spell 1 month PTD premonition of death	0	?	+	+	?	–	Sudden death
Generation IV	4 44F	Vague chest pains ×8 yrs palpitations mild dyspnea on exertion 2 years PTD	+	Upper limits of normal heart size	0	+	+	–	Sudden death
	5 49F	Active life no symptoms	0	Normal	+	+	+	Slight LV dilatation EF = 49%	Alive and well
Generation V	6 20M	None until fatigue flu like syndrome 4 days before death	+	?	?	?	?	–	Acute heart failure and unexpected death
	7 23F	None except for occasional vague chest pain active life	+	Normal	+	+	+	Normal EF = 48%	Alive and well
	8 24F	Active unrestricted life	+	Upper limits of normal heart size	+	+	+	Slight LV dilatation EF = 41%	Alive and well Mild LV dilatation and decreased contractility at cardiac catheterization
	9 26F	Active unrestricted life	+	Normal	+	0	+	–	Alive and well

Symbols and abbreviations ? = unknown + = present 0 = not present – = not done LV = left ventricle EF = ejection fraction PTD = prior to death

on relatives of the deceased woman including offspring, parents and grandparents on both sides of each family Heart disease and cardiac deaths were preponderant in one segment of the family and could be traced back five generations in a direct line A detailed historical search of this branch of the family was undertaken which included interviews of family members in three generations review of medical records and death certificates in all five generations and prospective medical examinations including electrocardiograms and chest x rays in all living family members Living family members who demonstrated any cardiac abnormality underwent

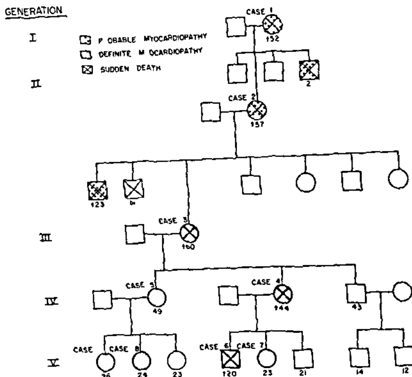


Fig 3 Family tree Case numbers refer to patients in text and on Table I Numbers below circles and squares refer to individual s age as of 19 6 or age at time of death

further evaluation including exercise stress testing echocardiography cardiac fluoroscopy and in one instance cardiac catheterization

Autopsy studies Complete autopsies were obtained on three first degree relatives in three different generations with cardiac disease The hearts were reviewed grossly and by light microscopy Histological stains performed included hematoxylin and eosin Congo Red Periodic acid Schiff phosphotungstic acid hematoxylin Verhoeff's elastin and sudan IV Electron microscopy was performed on formalin fixed tissue from two of the three hearts Conduction system was examined by a method described previously and adapted from Hudson

Results of a genealogical study

Family tree The family tree of the segment of the family under study is shown in Fig 3 The generations are designed I to V and clinical details of corresponding family members with definite or probable cardiomyopathy are summarized in Table I The proband the 44 year old woman (Case 4) is in the fourth generation of the family

Generation I The earliest recorded ancestor with cardiac disease in this family (Generation I) was the proband s great grandmother who died before the turn of the century at age 52 of fatty degeneration of the heart which was apparently a clinical diagnosis Little is known about her clinical details except that she had a long standing heart murmur and died at an unexpectedly early age Family records indicate that all her siblings (the exact number is not clear) lived into their 70 s or 80 s

Generation II The second generation of this family consisted of four children and two of them died cardiac deaths One a son died in his early 20 s also before 1900 of clinically diagnosed valvular disease of the heart The other a daughter (Case 2) died at age 57 of acute cardiac dilatation and chronic myocarditis and had a history of what were probably premature ventricular contractions The other two members of Generation II were apparently well living into old age

Generation III Seven offspring comprised the third generation of this family The mother (Case 3) of the index case was the third born of these seven siblings During a hospitalization approximately 20 years before her death she was noted to have a Wolff Parkinson White syndrome but led a generally vigorous active life At age 60 she died suddenly in her sleep In retrospect there was

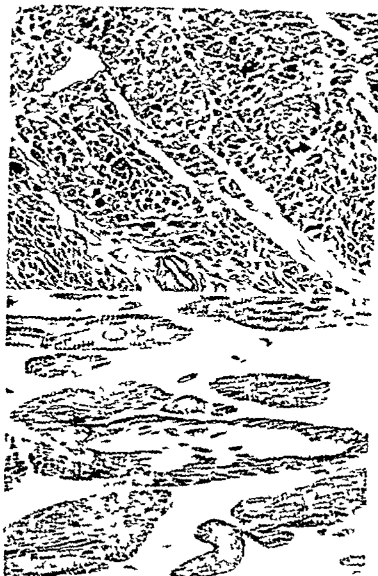


Fig 4 A Histologic sections of myocardium from mother of index case (No 3) showing extensive basophilic degeneration of the myocardium (Periodic acid Schiff stain original magnification ×125) B Longitudinal section of muscle cells shown in A with basophilic degeneration (Toluidine blue stain original magnification ×750)

some suspicion that she may have had a premonition of death and one month before her death she suffered a transient spell resembling petit mal' At autopsy the only significant abnormality was in her heart which had four chamber dilatation and a focally thickened and grayish white left ventricular endocardium The valves were minimally thickened and the coronary arteries widely patent Myocardium showed severe focal replacement fibrosis extensive basophilic degeneration (Fig 4) and prominent perinuclear lipofuchsin deposits present in many cardiac muscle cells Except for basophilic degeneration no other abnormalities of myocardial fine structure could be seen by electron microscopic examination of previously formalin fixed myocardium Death was attributed to a myocardial disease of unknown etiology

Although details of all her siblings are not available she, like her mother, had a brother who died in his early twenties of 'acute myocarditis and mitral insufficiency after three months of cardiac symptoms and associated systemic emboli Another brother died shortly after birth of "apnea neonatorum but it is not known whether cardiac disease was present There was no known cardiac disease in the other four members of this generation

Generation IV The fourth generation of this family consists of the three offspring of Case 3 the 60 year old woman who died in her sleep and includes the index case (Case 4) reported above who was the second oldest of her children The first member of this generation also a daughter (Case 5), has clinical findings similar to those of other family members including a short PR interval, nonspecific ST T wave changes, and exercise related premature ventricular contractions By echocardiogram she has a mildly dilated left ventricular cavity (5 5 cm) and no evidence of asymmetric hypertrophy She remains clinically well and asymptomatic at age 49 The third child in this generation a 43 year old male physician is well without evidence of cardiac abnormality by physical examination electrocardiogram electrocardiographic stress test or echocardiogram

Generation V Eight offspring of these three children comprise the fifth generation of this family and four of the eight have evidence of a cardiac abnormality similar to that present in the previous generations Within this fifth generation was the 20-year old son (Case 6) of the index case who died unexpectedly approximately one year before his mother This young college student had been in excellent general health and had recently passed a physical examination for admission to the lacrosse team Four days before his death he complained of unusual fatigue and subsequently developed a flu like illness Twenty four hours after admission to the college infirmary he died unexpectedly with left sided congestive heart failure At autopsy his heart weighing 540 grams showed biventricular dilatation and hypertrophy focal fibrosis and a thinned gray white endocardium The posterior tricuspid leaflet was adherent to the septal endocardium and the mitral valve had nodular thickening and rolling of its free margin The coronary arteries were normal Death was attributed to congestive heart failure caused by primary myocardial disease with endocardial fibroelastosis of unknown etiology

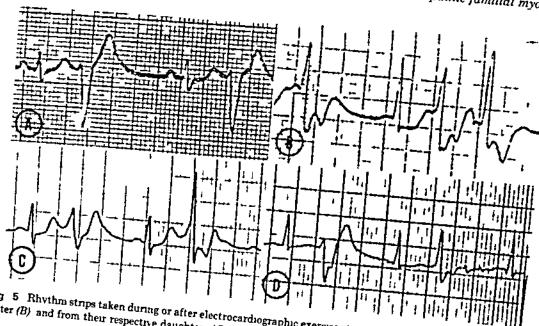


Fig 5 Rhythm strips taken during or after electrocardiographic exercise stress tests in the index case (A) and her sister (B) and from their respective daughters (C and D)

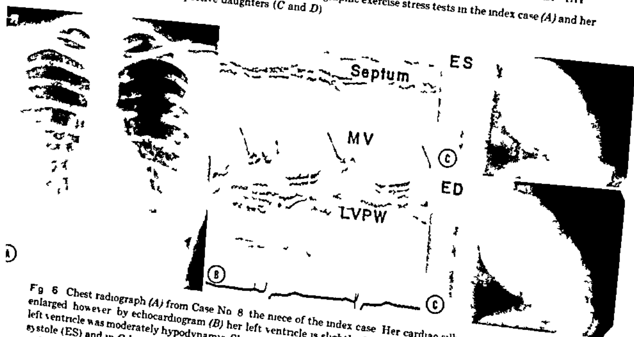


Fig 6 Chest radiograph (A) from Case No 8 the niece of the index case Her cardiac silhouette has never been enlarged however by echocardiogram (B) her left ventricle is slightly dilated and at cardiac catheterization her left ventricle was moderately hypodynamic Shown in C are frames from her left ventricular cineangiogram at end systole (ES) and in C *lower panel* at end diastole (ED) *MV* = mitral valve *LVPW* = left ventricular posterior wall

his deceased young man had two younger ngs His sister (Case 7) is an asymptomatic tic young woman who has had a precordial lic murmur since birth nonspecific ST and T abnormalities and exercise aggravated focal premature ventricular contractions 5) On several occasions she has had a short nterval (< 12 sec) with a normal QRS on Her heart is normal sized by chest raph and by echocardiogram the left ventricular cavity size is at the upper limits of normal The third sibling in this family is a young brother who is entirely free of any detectable cardiac abnormality by examination chest radiograph rest and stress electrocardiogram echocardiogram and Thallium 201 myocardial perfusion scan ' ' Also within the fifth generation of this family are the three children of Case 5 the sister of the index case two of whom have evidence of a similar myocardial disorder including systolic

murmurs, short PR intervals and minor ST segment abnormalities on electrocardiogram One of these two sisters (Case 8) also had a normal cardiac silhouette by chest radiograph and like her mother, aunt, and cousin (Case 7) multifocal premature ventricular contractions worsened by exercise By echo she has a mildly dilated and hypodynamic left ventricle with an ejection fraction of 41 per cent and no evidence of asymmetric hypertrophy (Fig 6) She was the only family member to undergo cardiac catheterization which demonstrated normal pressures a slightly enlarged left ventricle and generalized moderately impaired over all left ventricular contractility The two other members of Generation V are offspring of the unaffected brother of the index case and both are free of cardiac abnormalities by physical examination and noninvasive laboratory studies including electrocardiograms, chest radiographs and echocardiograms

Therapy In two members of Generation V (Cases 7 and 8) anti arrhythmic therapy was instituted After three baseline ECG stress tests and 24 hour Holter monitoring anti arrhythmic agents were started and repeat stress tests were performed Propranolol had little effect on the arrhythmias Both quinidine and diphenylhydantoin (Dilantin) were effective in suppressing the in exercise multifocal premature ventricular contractions and in decreasing postexercise extrasystoles Because of side effects related to quinidine dilantin was chosen for long term therapy in both patients Dilantin in a dose of 300 mg a day has been well tolerated and repeat stress tests at six months and one year s time have continued to show that ectopy is suppressed during and diminished after maximal exercise compared to the pretreatment studies

In contrast to these two patients anti arrhythmic therapy was unsuccessfully instituted in one member of generation IV (Case 5) Quinidine was not tolerated and resulted in syncope and Dilantin and procainamide had no effect on the frequency of her premature ventricular contractions

Discussion

A similar type of myocardiopathy distinctive both in its clinical presentation its course and its morphology developed in several members of at least three and possibly five generations of an otherwise healthy family The clinical manifestations of this familial myocardial disease are distinct from the usual forms of sporadic congestive cardiomyopathy Rather than being the chronic debilitating disorder lasting for a few years usually seen with idiopathic congestive cardiomyopathy this familial myocardiopathy ran a relatively long but benign subclinical course with those affected appearing healthy, vigorous and asymptomatic With most dilated congestive cardiomyopathies murmurs electrocardiographic abnormalities and arrhythmias become manifest along with symptoms of heart failure and signs of cardiac dilatation and do not precede them In the patients described here however precordial murmurs were most often detected in the first few years of life and conduction and rhythm disturbances were detected without associated heart failure or gross cardiac dilatation Even in the family members who died suddenly symptoms during life were minimal and signs of heart failure were present if at all, for only a brief time before death The clinical picture of this myocardiopathy also suggests that the same disorder may occur with variable severity in different affected family members Although two family members died prematurely in their 20 s and 40 s respectively, one lived into her 60 s suggesting that the disorder can be compatible with a normal or near normal life span

The familial pattern of this myocardial disease suggests an autosomal dominant mode of inheritance Of the 11 direct descendents of the mother of the index case six had evidence of cardiac abnormalities It is not clear however whether this disorder has a sex predominance Although female sex predominates in the affected family members women predominate in the offspring It is of note however that the one affected male who had the most severe form of the disease with death at age 20 also had congestive heart failure terminally The direct line descendents in Generations II III and V each had a brother dying in his early 20 s of cardiac failure In Generation III there was also a male sibling who died at birth but cardiac disease was not documented Although detailed medical records or autopsy information are only available on one of the three likely affected males one might wonder whether the cardiac abnormalities in this family were manifested in a milder form in the affected females

The over all picture of the familial myocardiopathy described here with autosomal dominant

inheritance and variable penetrance associated with murmurs electrocardiographic abnormalities a paucity of symptoms and sudden cardiac death appears superficially similar to the pattern of hypertrophic cardiomyopathy but echocardiographic cardiac catheterization and morphologic studies indicate that it is rather more akin to a congestive dilated type of cardiomyopathy Nonetheless morphologic observations on the family members from three different generations reaffirm the clinical impression that it comprises a most unusual form of dilated myocardiopathy The three hearts studied at autopsy showed similar morphologic abnormalities that varied only in degree Left ventricular hypertrophy and dilatation endocardial fibroelastosis and relative mitral insufficiency with secondary rolling and shortening of the leaflet margins was most prominent in the heart of the 20 year old intermediate in that of the 44 year old mother and most mild in his 61 year old grandmother suggesting again that the disease in its most severe form led to early death but in its milder form was consistent with a near normal life span The complex of morphologic features in these three hearts resembles both the idiopathic endocardial fibroelastosis of children and the idiopathic dilated myocardiopathy of adults Although the latter is rarely familial endocardial fibroelastosis of children[1, 6] may be inherited in an autosomal recessive pattern Unlike the familial myocardiopathy described here idiopathic endocardial fibroelastosis usually manifests itself within the first few years of life with symptoms of heart failure and at times conduction disturbances and leads to death within a matter of months to a few years Some patients have been reported to live to the second decade but these represent a distinct rarity

Although the cause of endocardial fibroelastosis is unsettled it may be a consequence and not a cause of left ventricular dilatation resulting from an underlying myocardial weakness[7, 1] Endocardial fibroelastosis is known to exist in a secondary phenomenon in a variety of congenital and acquired diseases associated with ventricular dilatation particularly when present early in life Similarly the endocardial fibroelastosis present in the three hearts under study may be a response to long standing mild ventricular dilatation as was documented angiographically in one clinically asymptomatic family member

An unusual morphologic feature of the myocardial disease in this family is the marked basophilic degeneration seen in the hearts of the grandmother and present to a moderate degree in the mother Basophilic degeneration[20, 21] is a focal myocardial disorder characterized by the deposition of a glycogen like granular substance within the central portions of myocardial fibers A mild degree of basophilic degeneration is present in over 80 per cent of hearts particularly with advanced age but there are certain disease entities in which basophilic degeneration exceeds that expected from age alone and may in such instances be related to myocardial dysfunction In myxedema heart disease in which there is a generalized myocardial hypodynamic state (generally believed to be sufficient for diminished metabolic demands) basophilic degeneration of myocardium is generally increased[1, 22] and may be related to abnormal glycogen metabolism Some patients with sporadic and familial idiopathic congestive myocardiopathy[1, 21] have also been reported to have extensive basophilic degeneration of myocardium but as in our patients it is uncertain whether the degenerative changes in myocardium are morphologic manifestations of an underlying metabolic defect causing muscle weakness or are unassocited or secondary changes

Another feature distinguishing this familial cardiomyopathy from the sporadic congestive myocardiopathy is the degree of myocardial fibrosis In idiopathic congestive cardiomyopathy fibrosis is usually minimal and limited mainly to the interstitium Frank replacement fibrosis unassociated with coronary artery disease is unusual although it may be seen in some rare myocardiopathies such as that associated with scleroderma The degree of myocardial fibrosis present in these three hearts exceeds that usually seen in idiopathic myocardial disease The fact that the fibrosis endocardial fibroelastosis and basophilic degeneration appear to become more prominent with age suggests that none of these is the primary disorder although they may in fact reflect an underlying primary myocardial disturbance

The arrhythmias and repolarization abnormalities the major clinical manifestations of this myocardiopathy showed a striking similarity among affected family members Familial arrhythmias and conduction disturbances have been reported in a variety of settings Families

with isolated repolarization abnormalities such as the long QT interval associated with sudden death have been reported [4-5] Idiopathic ventricular tachycardia has been described in siblings without detectable heart disease themselves who were part of a family with hereditary congestive myocardiopathy [6] There have also been reports of congenitally malformed conduction systems associated with sudden death in several family members with otherwise normal hearts,[8] and the mitral valve prolapse syndrome which may be associated with arrhythmias and sudden death in some families may be transmitted as an autosomal dominant trait [9-11]

The finding of a pre excitation syndrome in at least five of these family members described here may be important Since the first report of the Wolff Parkinson White syndrome [31] it has been recognized to be associated with certain congenital disorders including Ebstein s anomaly atrial septal defect, ventricular septal defect and tetralogy of Fallot [3-34] Although a number of reports have associated familial cardiomyopathies with Wolff Parkinson White syndrome [6, 31, 34] almost always the cardiomyopathy is of a hypertrophic variety A recent echocardiographic study demonstrated associated cardiac abnormalities in almost one quarter of patients with Wolff Parkinson White syndrome including two patients with hypertrophic cardiomyopathy and one with congestive cardiomyopathy [4] Since Wolff Parkinson White syndrome was first described other variants of the Wolff Parkinson White syndrome have been recognized as related pre excitation syndromes including the short PR interval with a normal QRS duration (Lown Ganong Levine syndrome) which is prevalent in the family described here Whether the pre excitation syndrome associated with idiopathic cardiomyopathy results from a specific nodal bypass tract or from intranodal abnormalities related to the underlying myopathic process is uncertain

Clinical and pathologic cardiac findings in this family raise questions about idiopathic non hypertrophic cardiomyopathy which are worthy of consideration First congestive cardiomyopathies may be familial and using the ECG as a screen one may be able to detect subtle subclinical abnormalities in the myocardium of first degree relatives of patients with seemingly sporadic congestive cardiomyopathy Only a detailed family search and prospective clinical evaluation of all living family members uncovered the striking inheritance pattern of the disorder described here Secondly, this family demonstrates that dilated cardiomyopathy like hypertrophic cardiomyopathy, may be subclinical, have a benign course and go virtually unrecognized during life And thirdly, the findings in this family point out that the class of disorders deemed idiopathic dilated cardiomyopathies are a heterogeneous group likely to be of multiple etiologies and pursuing varied clinical courses That dilated cardiomyopathies may be associated with an autosomal dominant pattern of inheritance and a relatively homogeneous clinical and pathologic expression suggests that a unitary biochemical defect yet to be discovered may lead to an intrinsic weakness of myocardial contraction

Summary

A peculiar non hypertrophic myocardiopathy is described which occurred in three and possibly five generations of a single family Clinical features included systolic murmurs electrocardiographic abnormalities and sudden cardiac death with a paucity of symptoms of cardiac dysfunction Pathological studies in three generations showed a striking similarity of cardiac findings including globular and dilated ventricles endocardial fibroelastosis and mitral valve thickening Myocardium in two showed basophilic degeneration and fibrosis A retrospective genealogic analysis and a prospective clinical evaluation of living family members suggested an autosomal dominant mode of inheritance with variable penetrance The cause of this heritable myocardiopathy is presumably a mutant gene the biochemical defect to which the mutant gene gives rise remains unknown

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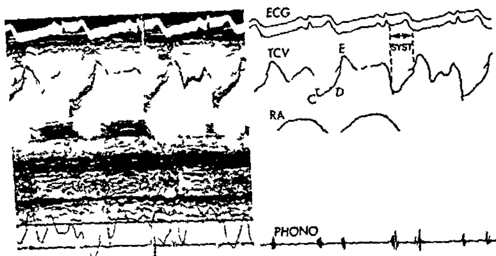


Fig 1 An example of the M mode echocardiographic pattern of the normal tricuspid valve showing the smooth gradual anterior motion during systole of the valve between the C and D points

Table I Echocardiographic pattern of tricuspid valve prolapse

Patient group	*Description*
I	Consecutive patients without mitral valve prolapse or congenital heart disease
II	Mitral valve prolapse (with adequate visualization of tricuspid valve)
III	Marfan's Syndrome patients with mitral valve prolapse
IV	Marfan's Syndrome patients without mitral prolapse

Table II Criteria

Echo must demonstrate

1 Maximum valve excursion where systolic portion is optimally seen
2 Complete visualization of tricuspid valve during systole
3 Exclude congenital heart syndromes
4 Pattern analogous to mitral prolapse patterns
   a Distinct midsystolic reversal of established anterior motion
   b Late systolic pattern acceptable only if posterior movement is 2 mm or greater from a horizontal line drawn connecting C and D points
   c Pansystolic
   d Early systolic posterior displacement acceptable only if pansystolic
   e Pattern seen on at least three non extrasystolic beats

systolic portion of the valve This could almost always be done in only one interspace and with one type of angulation in any given patient

Drawing on the experience of Markiewicz and colleagues DeMaria and others[6] we decided on the criteria listed in Table II for the demonstration of the pattern of tricuspid valve prolapse Points 4a and 4e are strict criteria that resulted from several years of experience with the mitral prolapse pattern This seems to be essentially analagous with that of tricuspid valve prolapse as suggested by others [7] and confirmed in the present study Fig 1 is an illustration of normal tricuspid valve motion by M mode echocardiography while Figs 2 through 4 are reproductions from some of our patients illustrating the criteria for an abnormal pattern as stated

Data analysis Groups were looked at individually for absolute incidence of tricuspid valve prolapse Group II containing the largest number of patients exhibiting the pattern of tricuspid valve prolapse was further analyzed for age sex and associated clinical characteristics Patients with mitral and tricuspid valve prolapse were compared to patients with mitral valve prolapse alone and p values were obtained using the χ analysis

Results

Occurrence Table III is a summary of our findings Group I patients revealed not one case of isolated tricuspid valve prolapse in 500 consecutive patients This finding was somewhat surprising in view of published reports of as high as 15 per cent incidence of angiographically demonstrated isolated tricuspid prolapse

Following completion of the analysis of this

Occurrence and significance of echocardiographically demonstrated tricuspid valve prolapse*

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Nelson B Schiller, M D
Richard Prasquier, M D
San Francisco Calif

Systolic prolapse of the mitral and tricuspid valves has been described both by angiography and noninvasively by echocardiography[1-3] The occurrence of prolapse of each valve individually as well as simultaneously has also been reported and speculation as to possible etiologic associations offered[1-4] However, the infrequent occurrence of the pattern of tricuspid prolapse as diagnosed by routine M mode echo in our laboratory coupled with the high incidence of this disorder reported angiographically[1] prompted us to investigate this finding more fully

Materials and methods

Patients We investigated a total of 562 patients by M mode echocardiography utilizing either a Picker EV X coupled with a Honeywell 1856 fiberoptic strip chart recorder or a Smith Kline Ekoview 20 A interfaced with an Irex strip chart recorder Two patients were additionally studied using the prototype of a 32 element phased array, 80 degree sector scanner developed by Varian Associates

There were four groups of patients (Table I) In Group I were 500 consecutive patients who had echocardiograms in our noninvasive laboratory and in whom the systolic portion of the tricuspid valve could be adequately visualized Excluded from this group were patients with mitral valve prolapse and patients with known congenital heart disease, including Ebstein's anomaly In Group II were 59 consecutive patients with echocardiographically proven mitral valve prolapse Six patients were discarded from this group due to inability to adequately visualize the systolic portion of the tricuspid valve according to criteria described below Group III (six patients) and Group IV (three patients) both had Marfan's syndrome, but with (III) and without (IV) mitral valve prolapse, respectively

Two patients with mitral and tricuspid valve prolapse underwent additional examination using the two dimensional real time sector scanner described above Their tricuspid valves were imaged in a transverse section through the base of the heart by directing the echo beam in the manner described by Henry and associates[10]

Criteria Patients were examined using standardized technique Patients were placed in the left lateral decubitus position and the transducer initially placed in the standard interspace[9] The tricuspid valve was then imaged in most cases, by inferior and slight medial angulation once the level of the aortic valve was visualized In some cases the valve was best imaged by visualizing the mitral just below the AV ring and then angulating almost directly medially until good tricuspid valve imaging was accomplished If both of these failed other interspaces were tried The objective was adequate visualization of the entire

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This work was supported in part by NHLBI Program Project Grant HL 06285

Received for publication June 23 1977

Accepted for publication Aug 12 1977

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Presented in part at the American Heart Association Meetings November 15 1976 Miami Beach Florida

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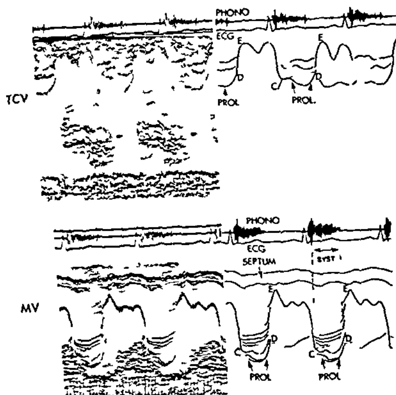


Fig 4 Mitral and tricuspid valve echoes taken from the same echocardiogram of a patient with mitral and tricuspid valve prolapse demonstrating marked similarities in prolapse pattern

small also suggests the apparent rarity of the pattern of tricuspid valve prolapse occurring by itself

Age and sex distribution There were a total of 17 males and 36 females in Group II (Table IV) This ratio of female predominance is typical with mitral prolapse Of the males three of 11 had mitral valve prolapse and tricuspid valve prolapse whereas fourteen of 42 had mitral prolapse alone—a difference that was not statistically significant Eight of the 11 females had both findings compared to 28 to 42 with mitral valve prolapse alone Again this difference was not significant However when both sexes are taken together and compared for age patients with mitral valve prolapse and tricuspid valve prolapse had a mean age of 57 years (± 15) whereas patients with mitral valve prolapse alone had a mean age of 37 (± 16) years This proved to be a significant difference at the p less than 05 level

Clinical features Correlations of the typical clinical features of mitral valve prolapse to the presence or absence of the additional finding of the pattern of tricuspid valve prolapse are shown in Table V Group II patients alone were considered because this group had the greatest number

Table III Echocardiographic pattern of tricuspid valve prolapse

Patient group	*Finding*	*% TVP*
I	Consecutive patients without mitral valve prolapse or congenital heart disease	0% (0/500)
II	Mitral valve prolapse (with adequate visualization of tricuspid valve)	21% (11/53)
III	Marfan s Syndrome patients with mitral valve prolapse	67 & (4/6)
IV	Marfan s Syndrome patients without mitral valve prolapse	0% (0/3)

of patients with tricuspid valve prolapse for analysis One patient with mitral valve and tricuspid valve prolapse had atypical chest pain Six of eleven with both findings had a systolic click and/or systolic murmur and three of eleven of these patients had a history of palpitations There was no statistically significant difference between these patients and patients exhibiting mitral prolapse alone

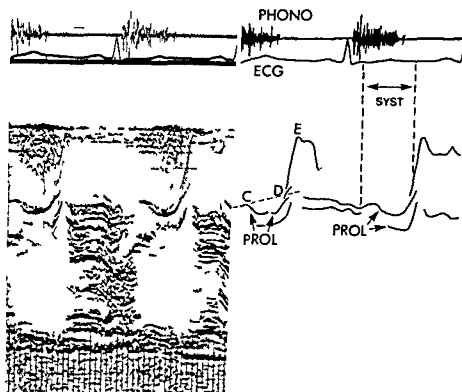


Fig 2 Example of late systolic prolapse demonstrating distinct midsystolic reversal of established anterior motion as well as greater than 2 mm of movement posterior to the CD line

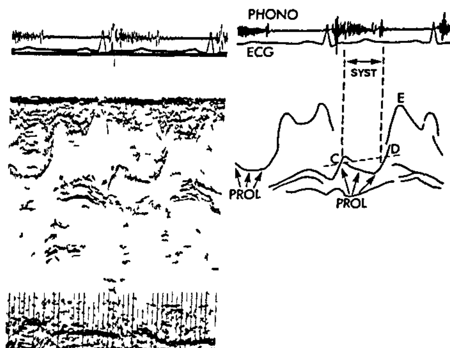


Fig 3 The pattern of pansystolic prolapse with greater than 2 mm of posterior systolic movement

study group, we have seen an occasional case of isolated tricuspid prolapse by echo but these instances were not apparently naturally occurring One case each with the pattern of tricuspid valve prolapse has been seen (a) following a right ventricular wound (b) with tricuspid valve vegetations, (c) with a large pericardial effusion and (d) in a patient with mitral regurgitation due to apparent chordal rupture

Group II patients revealed 11/53 or 21 per cent of patients with mitral valve prolapse who also had the pattern of tricuspid valve prolapse Group III Marfan s patients with mitral valve prolapse, revealed four of the six (67 per cent) to have an analagous pattern of tricuspid valve prolapse on echo None of the Group IV patients with Marfan s syndrome and no mitral prolapse had the tricuspid pattern This group although very

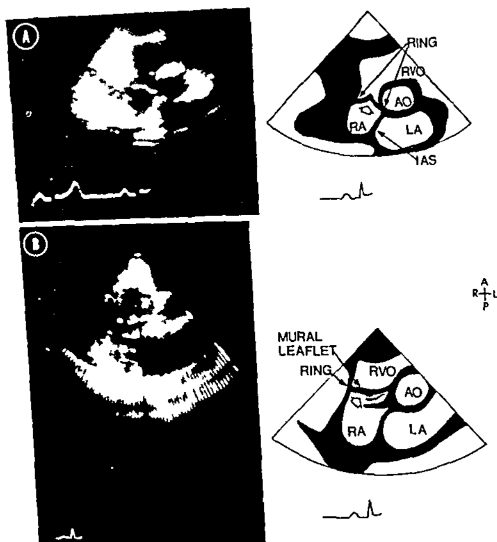


Fig 6A Two-dimensional sector scan taken in the short axis through the base of the heart of a normal individual. The frame was taken in early systole and demonstrates that the commissure of the septal and mural leaflets of the tricuspid valve lies slightly above the level of the bellies and ring attachment and is oriented toward the right ventricular outflow tract

Fig 6B Early systolic two-dimensional scan taken from a patient with M mode echo pattern of pansystolic tricuspid prolapse Note that the commissure is located slightly below the level of the ring attachment and that there is an extra set of echoes coming from the septal leaflet

studies on several patients the absence of any cases of isolated tricuspid valve prolapse in 500 consecutive patients and validation of the echocardiographic pattern by right ventricular angiogram in two patients one in and one outside (Fig 5) the study lent credence to our techniques and findings. Furthermore two tricuspid valve prolapse patients were also studied by two-dimensional echocardiography and were felt to have a pattern consistent with prolapse of the tricuspid valve toward the right atrium during systole (Fig 6)

Our study population is intended to investigate a different group of patients from those with congenital heart disease We expect that the findings and clinical applications likewise would not be similar These patients frequently have right ventricular enlargement which can actually

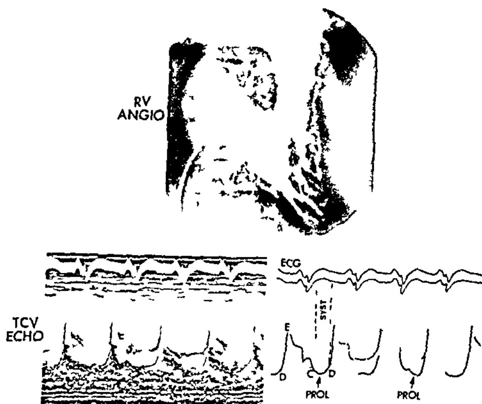


Fig 5 RV angiogram and M mode echo in same patient demonstrating tricuspid valve prolapse

Table IV Echocardiographic pattern of tricuspid valve prolapse Age and sex distribution—Group II patients

	MVP and TVP	*MVP only*	*P*
Age (yrs)	57 ± 15	37 ± 16	< 05
Male	27% (3/11)	33% (14/42)	NS
Female	73% (8/11)	67% (28/42)	NS

Table V Echocardiographic pattern of tricuspid valve prolapse Clinical features—Group II patients

	MVP + TVP	*MVP only*	*P*
a Atypical chest pain	9% (1/11)	10% (4/42)	NS
b Click and/or murmur	55% (6/11)	71% (30/42)	NS
c Palpitations	27% (3/11)	33% (14/42)	NS

Discussion

The present study of 562 patients represents one of the largest group of patients in whom the pattern of tricuspid valve prolapse has been systematically sought Our finding of 21 per cent occurrence of tricuspid valve prolapse in patients with mitral valve prolapse is less than half of the previously reported incidence of this association in both an angiographic series and a small echographic series[4] The true incidence of spontaneously occurring tricuspid valve prolapse however, can probably never be known because of absence of indications for right ventricular angiography in most patients coupled with the significant potential for artifact inherent in the echocardiographic detection of this type of anomaly The latter problem has been eloquently dealt with in mitral prolapse by Markiewicz and colleagues[5] and by Weiss and associates[6] When analagous criteria for transducer placement and angulation, as well as strict diagnostic criteria, are applied to the analysis of the tricuspid valve our experience suggests that reproducible findings can be achieved However the tricuspid valve remains more difficult to image adequately and inherently involves more transducer angulation Hence tricuspid valve imaging is unavoidably subject to more hazardous interpretation and therefore requires very careful extrapolation to clinical application Nevertheless with experience adequate and reliable visualization of the tricuspid valve and its anomalies is becoming easier and use of standardized technique in each laboratory should minimize such errors In our laboratory we often found that patients that had the pattern of tricuspid valve prolapse could sometimes have this pattern normalized with other transducer angulations However repetitive

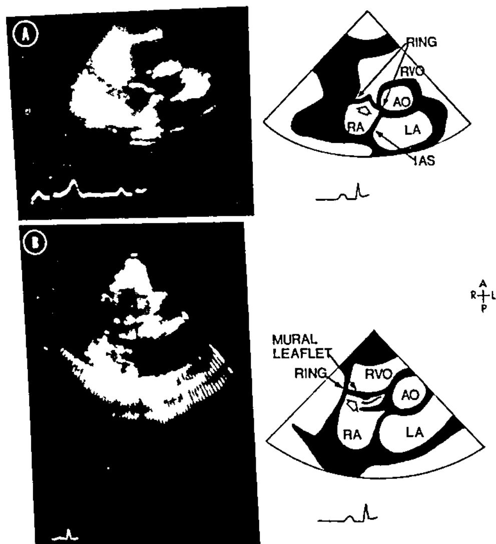


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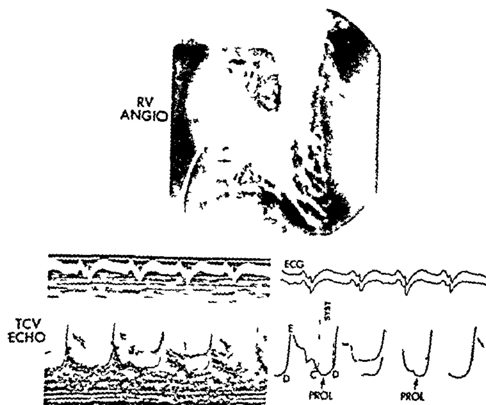


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	MVP + TVP	MVP only	P
a Atypical chest pain	9% (1/11)	10% (4/42)	NS
b Click and/or murmur	55% (6/11)	71% (30/42)	NS
c Palpitations	27% (3/11)	33% (14/42)	NS

Discussion

The present study of 562 patients represents one of the largest group of patients in whom the pattern of tricuspid valve prolapse has been systematically sought Our finding of 21 per cent occurrence of tricuspid valve prolapse in patients with mitral valve prolapse is less than half of the previously reported incidence of this association in both an angiographic series and a small echographic series The true incidence of spontaneously occurring tricuspid valve prolapse however can probably never be known because of absence of indications for right ventricular angiography in most patients coupled with the significant potential for artifact inherent in the echocardiographic detection of this type of anomaly The latter problem has been eloquently dealt with in mitral prolapse by Markiewicz and colleagues[5] and by Weiss and associates[6] When analagous criteria for transducer placement and angulation as well as strict diagnostic criteria are applied to the analysis of the tricuspid valve our experience suggests that reproducible findings can be achieved However the tricuspid valve remains more difficult to image adequately and inherently involves more transducer angulation Hence tricuspid valve imaging is unavoidably subject to more hazardous interpretation and therefore requires very careful extrapolation to clinical application Nevertheless with experience adequate and reliable visualization of the tricuspid valve and its anomalies is becoming easier and use of standardized technique in each laboratory should minimize such errors In our laboratory we often found that patients that had the pattern of tricuspid valve prolapse could sometimes have this pattern normalized with other transducer angulations However repetitive

Rapid sensitive detection of myoglobinemia by improved counterimmunoelectrophoresis in cases of acute myocardial infarction

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Kiss and Reinhart reported in 1956 that myoglobin (Mb) can be detected in the blood or urine of patients with acute myocardial infarction (AMI) However this has not been applied to clinical diagnosis because of the absence of a rapid and sensitive method for detection of Mb Occasionally AMI is difficult to diagnose at an early stage by means of electrocardiogram or measurement of serum enzyme activity A technique that can detect and provide an estimate of myocardial infarction size during the early stages should be useful

The counterimmunoelectrophoresis (CIE) technique for Mb although simple and rapid lacks sufficient sensitivity for AMI diagnosis[2] Thus we tried to improve the sensitivity of the Mb detection method by using water soluble nonionic polymer dextran which had been reported to enhance specific antigen-antibody reaction[3,5] and applied this modified CIE method to clinical cases

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Rece ed for publ tion J ly 5 19 7
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0002-8 03/78/0096-018 $00 40/0 © 19 8 The C V Mosby Co

Subjects and materials

We studied 48 patients admitted to our coronary care unit with AMI Blood samples were collected serially after admission The blood was left to coagulate and was then centrifuged at 4° C An aliquot of sodium azide was added to the serum samples which were then stored at −40° C and freeze thawed only once Materials used were agarose dextran of molecular weight 195 000 and Coomassie brilliant blue obtained from Nakarai Chemicals Ltd and anti human Mb serum obtained from the Behring Institute The veronal buffer had a pH of 8 6 and an ionic strength of 0 05 An MP-4 camera and type 105 film from the Polaroid Corporation were used

Methods

A CIE plate of 1 5 mm thickness was composed as shown in Table 1 Pairs of wells were made on the plate with the distance between the wells of each pair being 6 mm center to center The sample (10μl) was applied to the well on the cathode side and the anti serum was applied on

enhance the ability to image the tricuspid valve In addition, the attendant anatomical and physiological alterations frequently lead to increased valvular excursion, *multiple echoes and altered* structural relationships that would totally have redirected the viewpoint and purpose of the study

The remaining risk in this work lies in the possibility that a new disease' may have been discovered Our findings are strongly against this The pattern of tricuspid valve prolapse did not occur as an isolated finding When it did occur, it was always associated with mitral prolapse and in a greater percentage in patients with an underlying *connective tissue disorder (Marfan s) The one* significant finding of increasing occurrence with age, when taken together with the above, may provide a biological glimpse of the natural history of myxomatous degeneration Such a relation between the patterns of *mitral and tricuspid* prolapse had been suggested to us clinically in a patient with apparent endocarditis and mitral regurgitation from chordal rupture who also had tricuspid valve prolapse on the echo That such an association exists, although uncommon, could suggest an etiologic clue to the underlying pathology

In summary, the echocardiographic pattern of tricuspid valve prolapse is rare Its occurrence is almost always accompanied by mitral valve prolapse and likely represents part of the same clinical spectrum

Summary

Echocardiograms from 562 patients were examined for evidence of the pattern of tricuspid valve prolapse Criteria for the diagnosis can be established similar to those applicable to mitral prolapse In 500 consecutive patients without mitral valve prolapse, there were no cases of isolated tricuspid valve prolapse Eleven of 53 (21 per cent) patients with mitral valve prolapse also had tricuspid valve prolapse Four of six (67 per cent) patients with Marfan s syndrome and mitral valve prolapse also had tricuspid valve *prolapse The occurrence of this* echocardiographic pattern as an isolated finding as well as associated with mitral valve prolapse was significantly less than previous angiographic reports. Patients with both these findings tended to be older than those with mitral valve prolapse alone but clinically differed in no other way Use of standardized technique can minimize errors in diagnosis

The authors wish to thank Patricia Hart for the schematic drawing of Figs 6A and 6B and Mrs Sylvia T Smith and Mrs Kathleen G Hecker for their assistance in the preparation of this manuscript

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Table 1 Immunoelectrophoretic plate composition

Agarose	1 5 Gm
Veronal buffer (pH 8 6 ionic strength 0 05)	50 mL
Distilled water	50 ml
Sodium azide	0 1 Gm
Dextran (molecular weight 195 000)	3 0 Gm

cal application of this effect especially in the antigen or antibody excess zone has been suggested We managed to improve CIE sensitivity for detecting Mb using this effect

From a previous study[7] of serially collected blood samples from 21 AMI cases we have observed that in all patients there was an apparently elevated serum Mb level (above 150 ng /ml) within four hours from the onset of AMI Peak Mb concentration value averaged 1 146 ± 823 ng /ml while peak concentration occurred at 10 3 ± 4 8 (mean ± SD) hours Mb decreased exponentially by a half time of 6 7 ± 1 3 hours

Hibrawi and Blaker reported that CIE sensitivity to Mb was 2 000 ng /ml Since most myocardial infarction patients show values lower than this figure the method is not sensitive enough for the detection of myocardial infarction Our improved method is sufficiently sensitive thereby with the exception of small myocardial infarctions the diagnosis can be ascertained at bedside from blood samples taken within 10 hours from disease onset

In regard to the specificity of our method we studied 51 cases with heart disease other than AMI Only two of these were 1+ and ± the former being a resuscitated Adams Stokes patient and the latter a severe angina pectoris case Since it is well known that myoglobinemia is found in many other skeletal muscle diseases patients must be thoroughly checked for skeletal muscular damage We were impressed by the fact that the specificity of this method was sufficient for AMI diagnosis in a clinical setting

Summary

A counterimmunoelectrophoresis technique for detection of serum myoglobin (Mb) was improved using non ionic polymer dextran Precipitin lines were graded according to their strength which was ascertained by radioimmunoassay data By this method serum Mb in concentrations of 500 ng /ml before stain and of 200 ng /ml after stain were detected Electrophoretic time was 60 minutes Among 32 cases of acute myocardial infarction (AMI) whose blood samples were collected within 24 hours after disease onset precipitin lines were detected in 25 cases (78 per cent) before stain and 31 cases (97 per cent) after stain Considering the early peak concentration time (approximately 10 hours) of serum Mb after AMI onset diagnosis becomes more rapid and exact with this method especially in severe cases

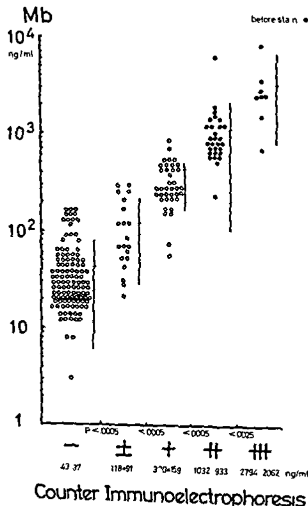


Fig 3 Myoglobin levels of precipitin lines divided into five classes according to line strength Myoglobin levels were measured by radioimmunoassay Mean +SD ng ml of myoglobin of each class is written at the bottom The phrase before stain in the figure means the detected precipitin line before staining on the photograph

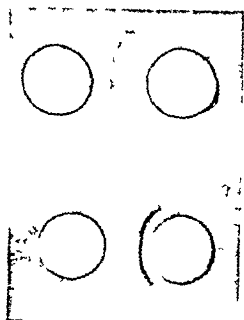


Fig 1 Immunoprecipitation enhancement Precipitin lines on the simple agarose plate *(top)* and on the agarose-dextran plate *(bottom)* of the same serum sample *(left side)*

the anode side The CIE was performed at 3 mA / cm constant current for 60 minutes in an electrophoretic chamber filled with the same veronal buffer at room temperature For easy detection of the precipitin line a photograph of the plate enlarged two and a half times was taken with an Mp 4 camera Subsequently the plate was deproteinized and stained with Coomassie brilliant blue as usual The Mb level of each serum sample was measured by radioimmunoassay able to detect 1 ng /ml of Mb[6]

Results

Precipitin lines easily visible as sharp lines concave toward the antibody reservoir were graded according to line strength — no line ± questionable line 1+ not sharp but easily visible line 2+ sharp line 3+ sharp thick line Fig 1 reveals the effect of 3 per cent (W/V) dextran and Fig 2 shows precipitin line examples The mean ± SD ng /ml of Mb levels measured by radioimmunoassay of each of the five above mentioned classes was 43 ± 37 118 ± 91 320 ± 159 1 032 ± 933 and 2 794 ± 2 062 respectively class differences were statistically significant Fig 3 presents these relationships

The sensitivity of this improved serum Mb CIE was approximately 200 ng /ml Before staining with Coomassie brilliant blue Mb above 500 ng / ml was detected on the photograph Forty eight samples in all which revealed precipitin lines

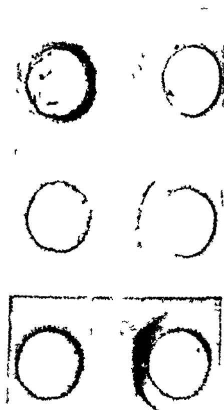


Fig 2 Graded precipitin lines by improved counterimmunoelectrophoresis top 1+ middle 2+ bottom 3+

stronger than 2+ also showed the lines before staining

Among the 48 cases admitted to our coronary care unit 31 cases (65 per cent) revealed positive precipitin lines of Mb of more than 1+ strength Among 32 cases whose blood samples were collected serially within 24 hours after AMI onset precipitin lines stronger than 1+ were detected in 31 (97 per cent) In enlarged photographs before staining 25 showed precipitin lines

These 32 cases were divided clinically into two groups—severe and less severe—of 17 and 15 cases respectively Among the 17 severe cases 14 showed precipitin lines before staining Of three negative cases two were sampled within four hours of the onset and one had a recurrent myocardial infarction that was thought to be small using other laboratory data

Discussion

The effect of specific antigen-antibody reaction enhancement by water soluble non ionic polymers such as dextran and carbowax has been known since 1968[1] although the mechanism of this effect was not ascertained[4] However clini

The importance of R on T phenomenon

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Early premature ventricular beats interrupting the T wave have long been considered hazardous in patients with organic heart disease.[1-3] They often lead to the development of ventricular tachycardia and fibrillation. In patients with acute myocardial infarction they are of particular concern and call for prompt institution of suppressive therapy. However, some recent data showed that the R on T phenomenon alone was not related to the development of ventricular tachycardia.[4] The purpose of this study is to re-examine the role of early premature ventricular contractions in the genesis of ventricular tachycardia in a group of unselected patients.

Methods

Forty-four consecutive patients in whom the *onset* of ventricular tachycardia was recorded were studied. They consisted of both hospitalized and clinic patients at the University of Cincinnati Medical Center Hospitals. The electrocardiograms were obtained by either the conventional electrocardiograph, bedside monitor in the Cardiac Care Unit, or Holter monitor. They were observed by the authors during a 3 year period but do not represent the total number of such patients in this institution during this period. Although a much larger number of patients with ventricular tachycardia was seen, they were not included in this study unless the onset of the tachycardia was demonstrated and their electrocardiograms met all of the following criteria:

1. The basic rhythm was sinus in origin.
2. The paroxysm consisted of three or more abnormal and wide QRS complexes which were different in morphology from those of the sinus beats.
3. The tachycardia had a rate greater than 110/minute.
4. There was no *premature* P wave preceding the onset of the tachycardia.
5. In addition, one or more of the following findings should also be present during the paroxysm of tachycardia:
   - A. Atrioventricular dissociation
   - B. Fusion beat
   - C. Capture beat, or
   - D. Isolated premature ventricular contraction in the same lead having the same QRS morphology as that of the tachycardia.

Cases with supraventricular tachyarrhythmia such as atrial fibrillation, atrial flutter, or paroxysmal atrial tachycardia as the basic rhythm were excluded because the possibility of aberrant ventricular conduction was more difficult to rule out in their presence.

The electrocardiographic analysis consisted of the determination of:

1. The coupling time or R-R' interval, which is the duration from the preceding R wave of sinus origin and the R wave of the premature ventricular contraction (R') initiating the tachycardia.
2. The Q-T interval of the normal sinus beats.
3. The prematurity index or R-R'/Q-T; a prematurity index of less than 1.0 is considered to be the equivalent of the R on T phenomenon.
4. The rate of the ventricular tachycardia.

If more than one episode was recorded in the same patient, the episode with the shortest R-R' interval was used, realizing that such a selection

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Supported in part by a grant from the Southwestern Ohio Chapter of the American Heart Association.

Received for publication July [illegible]8, 197[illegible].

Accepted for publication Sept. [illegible]1, 19[illegible].

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The authors wish to acknowledge the advice of Dr Susumu Sugai Associate Professor Kanazawa Medical College

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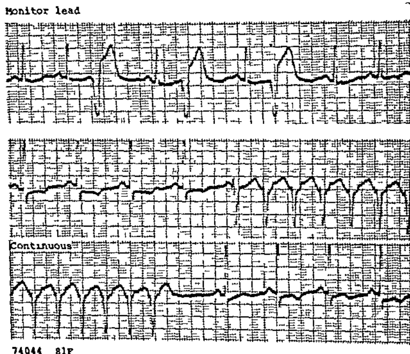


Fig 1 Ventricular tachycardia initiated by a late premature ventricular contraction which interrupts the P wave of the following sinus beat Retrograde capture of the atria is probably present beginning with the second complex of the tachycardia *In the top strip* premature ventricular contractions with the R on T phenomenon are not associated with the development of ventricular tachycardia (Isolated premature ventricular contractions having the same QRS T morphology as that during the tachycardia are also present but not shown)

sinus P wave One of such cases is illustrated in Fig 1

Twenty five of the patients also had isolated premature ventricular contractions with different coupling time In 14 their R R /Q T ratio was smaller than the R R /Q T ratio of the ventricular ectopic beats initiating the ventricular tachycardia In four the premature ventricular contractions interrupted the preceding T wave without the development of ventricular tachycardia while the ventricular tachycardia of these patients was initiated by a premature ventricular contraction appearing later in the cycle (Fig 1)

Discussion

In 1949 Smirk reported 17 patients with interruption of the T wave by a premature ventricular complex Three of the patients died suddenly Later he described a larger series of patients with various types of heart disease and the R on T phenomenon which he regarded as a poor prognostic sign Lown and associates subsequently emphasized the danger of early premature ventricular beats in patients with acute myocardial infarction Examples were given to illustrate the precipitation of ventricular tachycardia by *early* premature ventricular contractions in contrast with the absence of such event with *late* premature ventricular contractions Dolara[5] described three cases of ventricular tachycardia and fibrillation initiated by early premature ventricular contractions Gutierrez and colleagues reported 26 episodes of ventricular tachycardia or ventricular fibrillation in 12 patients in whom the R on T phenomenon was demonstrated In the experimental animals electrical stimuli applied to the ventricle during a period of the T wave (the vulnerable period) are effective in inducing rapid repetitive responses and ventricular fibrillation[8] This is particularly true in the presence of severe myocardial ischemia It is now a general clinical practice to regard the R on T phenomenon as one of the indications for prompt initiation of suppressive therapy in patients with acute myocardial infarction

Bleifer and associates[7] studied the relationship of the R on T phenomenon to the development of ventricular tachycardia in ambulatory patients with ischemic heart disease using the Holter monitor None of the 34 cases who had the

Table I Clinical diagnosis in the 44 patients with ventricular tachycardia

Diagnosis	No of patients
Coronary artery disease	20
Acute myocardial infarction	6
Cardiomyopathy	5
Hypertensive heart disease	5
Idiopathic ventricular tachycardia	3
Mitral valve prolapse	2
Rheumatic heart disease	1
Heart disease of uncertain etiology	8
Total	44

Table II Distribution of the prematurity index (R-R/Q-T) of the premature ventricular contractions initiating ventricular tachycardia

Prematurity Index (R-R/Q-T)	No of patients
< 1.0	6
1.0-1.19	12
1.20-1.39	13
1.40-1.59	7
1.60-1.79	3
1.80-1.99	1
2.0-2.1	2
Total	44

may increase the relative frequency of the R on T phenomenon in the group. In patients who had isolated premature ventricular contractions in the same tracing, their prematurity indices were also calculated.

The following clinical data of the patients were obtained: age, sex, clinical diagnosis, cardiac drug or drugs (including digitalis, quinidine, procainamide, lidocaine, propranolol) received at the time of ventricular tachycardia, presence or absence of electrolyte imbalance.

Results

Among the 44 patients with ventricular tachycardia, 23 were male and 21 were female. Their age ranged from 14 to 85 years with a mean age of 58 years. The types of associated heart disease are listed in Table I. Twenty of the patients had coronary artery disease with eight of them having acute myocardial infarction at the time of the electrocardiographic recording. Others had cardiomyopathy, hypertensive heart disease, mitral valve prolapse, rheumatic heart disease, heart disease of undetermined etiology, and idiopathic ventricular tachycardia. Seventeen patients were receiving no cardiac drug at the time of the paroxysmal ventricular tachycardia. Seventeen patients were taking digitalis, but in only one of them digitalis was considered the possible cause of the arrhythmia. Fifteen patients were receiving one or more of the other cardiac drugs with or without digitalis. There was no evidence of electrolyte imbalance in the entire group except the patient with possible digitalis intoxication had a serum potassium level of 3.1 mEq/L.

In addition to the criteria (paragraphs 1 to 4) described under *Methods* for the electrocardiographic diagnosis of ventricular tachycardia, A-V dissociation was present in 32 patients. One patient had ventricular capture beats and six patients had fusion beats. Another patient had both capture and fusion beats. All but one of these eight cases also had evidence of A-V dissociation. Twenty-two patients had premature ventricular contractions with similar morphology in the same lead that recorded the ventricular tachycardia. In 10 of these patients evidence of A-V dissociation was not demonstrated.

In one half of the 44 patients the paroxysm consisted of five or more ventricular complexes. In the entire group the ventricular rate varied between 115 to 300/minute with an average rate of 160/minute. The coupling time of the premature ventricular contractions initiating the tachycardia (R-R interval) had a range between 0.20 to 0.80 sec. The prematurity index (R-R'/Q-T) was between 0.6 and 2.1. Only six patients had an index less than 1.0 and, therefore, the R on T phenomenon. One of these patients had acute myocardial infarction, one had Prinzmetal angina. The other four patients had cardiomyopathy, mitral valve prolapse, organic heart disease of unknown etiology, and idiopathic ventricular tachycardia respectively. Four cases had an index of 1.0. All of them had coronary artery disease with two having acute myocardial infarction. The distribution of the patients with different degrees of prematurity of the initiating premature ventricular contraction is depicted in Table II. It is apparent that relatively late premature ventricular contractions were responsible for the onset of ventricular tachycardia in the majority of instances. Indeed, in 16 cases the ventricular tachycardia began after the onset of the next

Experimental and laboratory reports

Postextrasystolic aortic pressure pulse response in coronary artery disease

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The greatest interest in aortic pressure-pulse contour change after extrasystolic beats has been in hypertrophic subaortic stenosis.[1] Here the postextrasystolic beat manifests a decrease in pulse pressure when compared to beats preceding the extrasystole. It had generally been our impression that the normal postextrasystolic response is accompanied not only by an increased pulse pressure but also by an increased systolic pressure as well. During a previous study of the effect of postextrasystolic potentiation in patients with coronary artery disease,[2] we observed that it was unusual that the postextrasystolic beat generated a systolic pressure higher than in preceding beats. Beck and associates[3] in patients with varying types of heart disease observed a postextrasystolic increase in the left ventricular systolic pressure. Such responses were seen in left ventricular outflow obstruction, myocardial failure, and in the volume overloaded left ventricle. Furthermore, Beck observed that the systolic pressure response after an extrasystolic beat was different in left and right ventricles in "normals." In view of the observations of Beck and co-workers, as well as our continued interest in postextrasystolic potentiation, we evaluated the postextrasystolic aortic pressure-pulse contour in a consecutive series of patients with coronary artery disease and related the response of the systolic pressure to left ventricular function.

Material and methods

One hundred consecutive patients referred for angina pectoris underwent a complete evaluation including a complete history and physical examination, standard 12 lead electrocardiogram, posterior-anterior and lateral chest x-ray films, and a complete right and left heart catheterization including left ventricular angiogram and selective coronary arteriography. Excluded were all patients without demonstratable coronary artery disease or with valvular heart disease. The diagnosis of a prior myocardial infarction on the electrocardiogram was made on the basis of accepted criteria,[4] while cardiomegaly on x-ray was diagnosed by a radiologist. Hemodynamic studies were performed by methods and criteria previously published.[2]

After completion of hemodynamic studies, a pigtail catheter (Cordis F 8) was positioned in the ascending aorta for obtaining the pressure-pulse contours, which were recorded simultaneously with an electrocardiogram. Aortic pressure was obtained with a balanced Statham strain gauge transducer (P23Db) and recorded on an Electronics for Medicine recorder (Model DR 16) at a paper speed of 25 or 100 mm./sec. with 100 or 40 msec. time lines. The aortic pressure pulse was recorded while single ventricular extrasystoles were induced by a catheter in the right ventricle. The time between the R wave of the last

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Received for publication Jan. 14, 1977.

Accepted for publication July 5, 1977.

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0002-8703/78/0296-0195$00.80/0

R on T phenomenon alone developed ventricular tachycardia However, there was a substantial incidence of ventricular tachycardia when both the R on T phenomenon and pairing of the premature ventricular contractions occurred In patients with acute myocardial infarction de Soyza and co workers failed to find any significant difference between the mean coupling interval of the premature ventricular contractions initiating ventricular tachycardia and those that did not initiate tachycardia More recently, Winkle and co workers[10] studied 23 ambulatory patients with various types of heart disease who had a total of 94 episodes of ventricular tachycardia The R on T phenomenon was observed in only 15 per cent of the episodes

Our data show that in only six of the 44 unselected patients the ventricular tachycardia was initiated by an early premature ventricular contraction In a substantial number of patients (16) the ventricular tachycardia was precipitated by very late premature ventricular contractions appearing after the onset of the next sinus P wave These findings were observed in both patients with acute myocardial infarction and patients with other types of heart disease The results from this and the other studies raise considerable doubts as to the relative importance of the R on T phenomenon in the genesis of paroxysmal ventricular tachycardia

Two proposed electrophysiological mechanisms are most commonly used to explain the production of premature ventricular contractions and ventricular tachycardia One of them is the reentry theory There is a local area of impaired excitability and conductivity in the ventricular myocardium which is depolarized by the impulse of the basic cardiac rhythm only after a considerable delay When it is finally activated it generates a wave of excitation which finds some of its surrounding myocardium being now excitable resulting in a premature ectopic beat A circus movement may be established causing repetitive tachycardia It is believed that this mechanism is responsible for the appearance of early premature ventricular contractions as these premature ventricular contractions are related to the preceding complex and are initiated as soon as the tissue recovers from its excitability [8] The second theory suggests that there is an enhanced automaticity of the His Purkinje fibers This mechanism is probably responsible for those premature ventricular contractions with relatively long coupling time, as time should be allowed for the Purkinje fibers to be repolarized before they begin their diastolic slow depolarization Since most of our cases of ventricular tachycardia began with a late premature ventricular contraction it is possible that increased automaticity of the Purkinje fibers is a more important mechanism in the initiation although not necessarily perpetuation, of the ventricular tachyarrhythmia

Summary

The onset of ventricular tachycardia was examined in 44 patients with various types of heart disease In only six patients (14 per cent) the ventricular tachycardia was initiated by an ectopic ventricular complex interrupting the T wave The findings suggest that the importance of R on T phenomenon may have been over emphasized

The authors wish to thank Dr Noble O Fowler for reviewing the manuscript and his helpful suggestions

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Fig 3 Four series of extrasystolic beats (*A*,*B* *C*,*D*) with progressive lengthening of the coupling interval (numbers *below each figure*) *demonstrating a response* typical for group I after the postextrasystolic beat with lengthening of the coupling interval.

Table I Clinical profile and angiographic findings

Groups	IA		IB		IIA		IIB	
	No	*(%)*	*No*	*(%)*	*No*	*(%)*	*No*	*(%)*
Number	45		40		12		3	
Age (yrs) (Mean ± 1 SD)	54 ± 8		54 ± 6		57 ± 11		53 ± 3	
Sex (M/F)	37/8		31/9		11/1		3/0	
Duration of symptoms (Mean ± 1 SD)	3 3 ± 1 1		3 0 ± 1 1		3 9 ± 2 1		4 0 ± 0 8	
Congestive heart failure	1	(2)	0	(0)	8	(67)	3	(100)
Cardiomegaly (by x ray)	1	(2)	2	(5)	6	(50)	3	(100)
Myocardial infarction (by ECG)	21	(47)	14	(35)	8	(67)	3	(100)
Coronary artery disease								
Number of vessels								
Single	9	(20)	12	(30)	1	(17)		
Double	16	(36)	10	(25)	0	(0)		
Triple	20	(44)	18	(45)	11	(83)	3	(100)
Abnormal left ventricular contractile pattern	30	(67)	25	(62)	12	(100)	3	(100)

assistance of a statistician utilizing a programmable calculator and either the chi square statistic or the unpaired Student t test

Results

The 100 coronary artery disease patients studied manifested four distinct patterns of aortic systolic pressure in the immediate postextrasystolic beat Contractions preceding the extrasystolic beat were designed as control beats Group IA consisted of 45 patients demonstrating a *lower* systolic pressure (<5 mm Hg) in the postextrasystolic beat as compared to control (Fig 1*A* *arrow*) After two *to six* beats the pressure returned to levels observed prior to the extrasystole Group IB consisted of 40 patients demonstrating a systolic pressure in the postextrasystolic beat essentially *equal* (±5 mm Hg) to *control* (Fig 1*B* *arrow*) Group IIA contained 12 patients who showed an *increase* in the systolic pressure (>5 mm Hg but almost invariably 10 or more) as compared to control (Fig 2*A* *arrow*) with return either immediately *on the second* beat to control levels or gradually over the next *two to four beats* In four patients pressure generated in the second postextrasystolic beat was *less* than control but all subsequent beats were similar to control The response in these four patients represented a transition to group IIB response *where in all* three patients the increase in postextrasystolic systolic pressure was followed by *four* to six beats demonstrating pulsus alternans (Fig 2*B*) The coupling index observed in groups IA and IB were 0 32 ± 0 07 and 0 33 ± 0 07

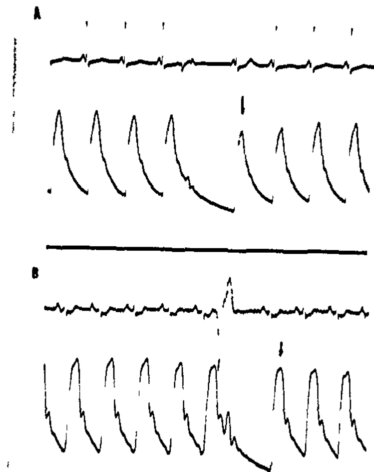


Fig 1 A and B Aortic pressure-pulse response after an extrasystole in group IA (*A*) and group IB (*B*) *The arrow* points to the postextrasystolic beat Note in *A* that the systolic pressure in the postextrasystolic beat is less than in beats preceding the extrasystole while in *B* the postextrasys tolic pressure is the same as that of the beats preceding the extrasystole

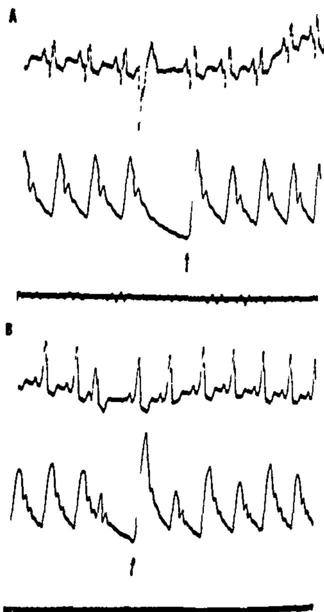


Fig 2 A and B Aortic pressure-pulse response after an extrasystole in group IIA (*A*) and IIB (*B*) *The arrow* points to the postextrasystolic beat which in both cases has a higher systolic pressure as compared to beats preceding the extrasys tole Note furthermore in *B* that following the first postextra systolic beat there is pulsus alternans

conducted sinus beat and the extra systole (R_1 Ex) was determined (coupling interval) The time between R_1 and the first sinus conducted R wave (R_2) after the extra systole was then determined (R_1 R) The latter interval (R_1 R_2) comprises the coupling interval and the compensatory pause The coupling index was defined as R_1 Ex/R_1 R_2 A value close to 0 5 msec would represent an *interpolated beat*

Left ventricular cineangiograms were then obtained in the right anterior oblique position by *injecting 0 50 to 0 75 ml /Kg of 75 per cent sodium* meglumine diatrizoate over a two second interval using a power injector (Viamonte Hobbs) via a pigtail *catheter positioned in the left ventricle A* grid of known dimensions was positioned at the approximate location of the left ventricle and a short film strip was taken *to permit correction of* errors due to magnification This was followed by selective coronary angiography performed in multiple projections using the Judkins tech nique

Left ventricular volumes were obtained using the area-length method[5] and regression equation of Kasser and Kennedy[6] by techniques previously *described*[2] The left ventricular end diastolic volume index and ejection fraction determined in 20 patients with normal left ventricles using this *method* were 69 ± 19 ml /M[2] and 0 68 ± 0 10 respectively An abnormal left ventricular con tractile pattern was defined as localized absence (akinesia) or diminished (hypokinesia) wall move ment or generalized hypokinesia[7]

All data were analyzed statistically with the

All three patients in group IIB had a history of congestive heart failure as well as cardiomegaly, on x ray and electrocardiographic evidence of both anterior and inferior myocardial infarctions (Table I)

Selective coronary arteriography (Table I) revealed that 83 per cent of the patients in group IIA had triple vessel coronary artery disease as compared to 44 and 45 per cent in groups IA and IB respectively ($p < 0.01$) Left ventricular angiography revealed that all patients in group IIA had an abnormal left ventricular contractile pattern as compared to 67 and 62 per cent in groups IA and IB respectively ($p < 0.025$) Triple vessel disease and an abnormal left ventricular contractile pattern were present in all three patients in group IIB (Table I)

The mean left ventricular end diastolic pressure for groups IA and IB were 14 ± 6 and 12 ± 7 mm Hg respectively which for both groups was significantly ($p < 0.025$) less than the 19 ± 9 mm Hg observed in group IIA The mean left ventricular end diastolic pressure for the three patients in group IIB was 31 mm Hg The mean heart rates and mean aortic pressures at the time of study revealed no significant group differences Although not specifically measured the postextrasystolic beat demonstrated a lower diastolic and a wider pulse pressure when compared to the control thus absolute group mean values for these parameters could not be evaluated Comparing groups IA and IB with each other for cardiac output (Fig 4) stroke volume (Fig 5) end diastolic volume (Fig 6) and ejection fraction (Fig 7) showed no significant differences However when comparing these two groups with the patients in group IIA significant differences were revealed Two thirds of the patients in group IIA had an abnormal cardiac output (2.5 L/min/M^2) with a mean value of 2.2 ± 0.6 (L/min/M^2) as compared ($p < 0.01$) to 2.8 ± 0.5 and 2.9 ± 0.5 L/min/M^2 in groups IA and IB respectively (Fig 4) Similarly the stroke volume was 30 ± 10 ml/M^2 in group IIA which was significantly ($p < 0.005$) less than observed in groups IA and IB (Fig 5) The mean end diastolic volume (ml/M^2) observed in group IIA was 102 ± 28 as compared ($p < 0.001$) to 69 ± 11 observed in group IA and 65 ± 12 found in group IB (Fig 6) Finally all the patients in group IIA had an abnormal ejection fraction (< 0.5) the group mean being 0.30 ± 0.08 (Fig 7) which was

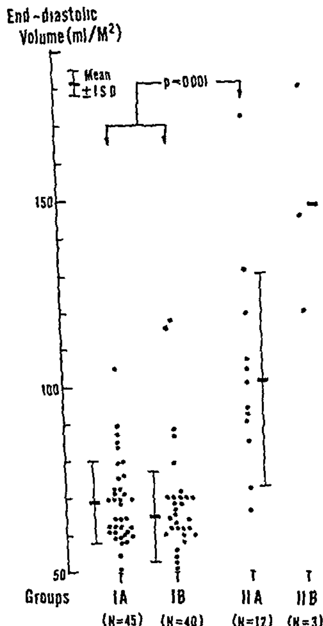


Fig 6 End-diastolic volume in the four groups of patients Each point represents an individual patient with the horizontal bar being the mean for each group N = number of patients

significantly ($p < 0.001$) less than 0.57 ± 0.11 and 0.59 ± 0.11 observed in groups IA and IB respectively All three patients in group IIB had abnormally low cardiac outputs (Fig 4) and ejection fractions (Fig 7) as well as abnormally high (> 100 ml/M^2) end-diastolic volumes (Fig 6)

Discussion

The present study confirms the findings reported by Beck and associates[3] on patients with

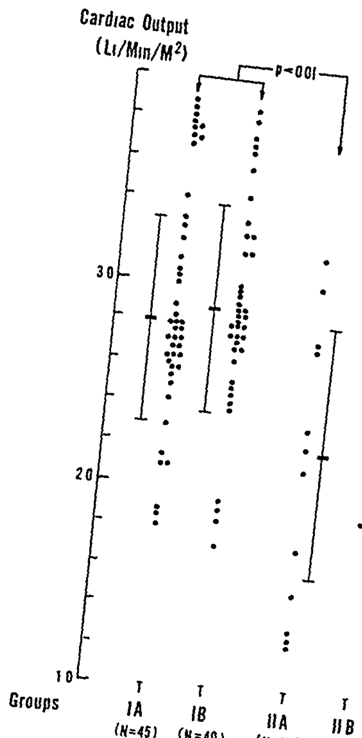


Fig 4 Cardiac output in the four groups of patients Each point represents an individual patient with the horizontal bar being the mean for each group N = number of patients

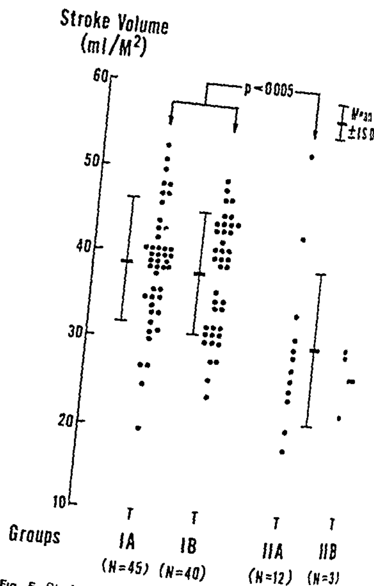


Fig 5 Stroke volume in the four groups of patients Each point represents an individual patient with the horizontal bar being the mean for each group N = number of patients

respectively, which was not significantly different to 0 36 ± 0 04 in group IIA The mean coupling index in the three patients of group IIB was 0 34 In two patients in group IA and three patients in group IB changing the coupling index with pacemaker induced extrasystoles did not change the response i e they still had a group I response (Fig 3) whereas in one patient in Group IIA a coupling index greater than 0 4 produced variable responses The response to two or three consecutive extrasystoles was variable in groups IA and IB whereas such beats did not alter the distinct postextrasystolic pressure response in groups IIA and IIB

The ages of the patients studied and duration of their symptoms in each of the four groups described above showed no significant differences (Table I) A history of congestive heart failure was significantly ($p < 0.001$) more frequent in group IIA as compared to both groups IA and IB (Table I) Similarly enlarged heart on x ray was more frequent ($p < 0.005$) in group IIA when compared to either group IA or IB (Table I) Eleven patients (83 per cent) in group IIA had electrocardiographic evidence of a prior myocardial infarction as compared to 21 (47 per cent) and 14 (35 per cent) in groups IA and IB respectively ($p < 0.01$) The location of the infarction by electrocardiogram was not different in the three groups of patients (IA, IB and IIA)

All three patients in group IIB had a history of congestive heart failure as well as cardiomegaly on x ray and electrocardiographic evidence of both anterior and inferior myocardial infarctions (Table I)

Selective coronary arteriography (Table I) revealed that 83 per cent of the patients in group IIA had triple vessel coronary artery disease as compared to 44 and 45 per cent in groups IA and IB respectively ($p < 0\,01$) Left ventricular angiography revealed that all patients in group IIA had an abnormal left ventricular contractile pattern as compared to 67 and 62 per cent in groups IA and IB respectively ($p < 0\,025$) Triple vessel disease and an abnormal left ventricular contractile pattern were present in all three patients in group IIB (Table I)

The mean left ventricular end diastolic pressure for groups IA and IB were 14 ± 6 and 12 ± 7 mm Hg respectively which for both groups was significantly ($p < 0\,025$) less than the 19 ± 9 mm Hg observed in group IIA The mean left ventricular end diastolic pressure for the three patients in group IIB was 31 mm Hg The mean heart rates and mean aortic pressures at the time of study revealed no significant group differences Although not specifically measured the postextrasystolic beat demonstrated a lower diastolic and a wider pulse pressure when compared to the control thus absolute group mean values for these parameters could not be evaluated Comparing groups IA and IB with each other for cardiac output (Fig 4) stroke volume (Fig 5) end-diastolic volume (Fig 6) and ejection fraction (Fig 7) showed no significant differences However when comparing these two groups with the patients in group IIA significant differences were revealed Two thirds of the patients in group IIA had an abnormal cardiac output (2 5 L/min/M²) with a mean value of $2.2 \pm 0\,6$ (L/min/M²) as compared ($p < 0\,01$) to $2\,8 \pm 0\,5$ and $2\,9 \pm 0\,5$ L/min/M² in groups IA and IB respectively (Fig 4) Similarly the stroke volume was 30 ± 10 ml/M² in group IIA which was significantly ($p < 0\,005$) less than observed in groups IA and IB (Fig 5) The mean end diastolic volume (ml/M²) observed in group IIA was 102 ± 28 as compared ($p < 0\,001$) to 69 ± 11 observed in group IA and 65 ± 12 found in group IB (Fig 6) Finally all the patients in group IIA had an abnormal ejection fraction ($< 0\,5$) the group mean being $0\,30 \pm 0\,08$ (Fig 7) which was

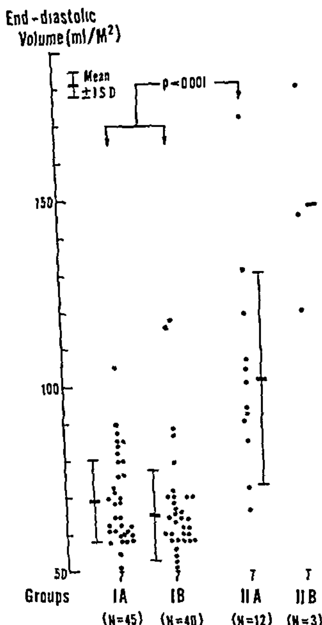


Fig 6 End-diastolic volume in the four groups of patients. Each point represents an individual patient with the horizontal bar being the mean for each group N = number of patients

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Discussion

The present study confirms the findings reported by Beck and associates[1] on patients with

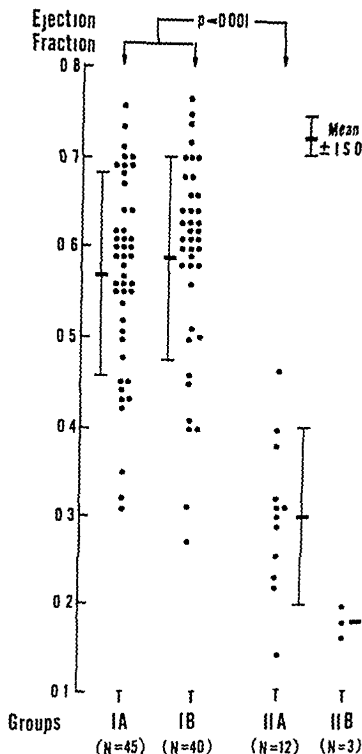


Fig 7 Ejection fraction in the four groups of patients Each point represents an individual patient with the horizontal bar being the mean for each group N = number of patients

various types of heart disease The "normal" response after an extrasystole (a decrease or no change in aortic systolic pressure) was noted in 85 per cent of our patients with coronary artery disease (groups IA and IB) This contrasts sharply (Fig 8) with the 15 patients in groups IIA and IIB Here the postextrasystolic beat had a higher aortic systolic pressure than did beats preceding the extrasystole and these patients had a clinical picture characterized by a history of congestive heart failure, cardiomegaly and evidence of prior transmural myocardial infarction (Table I) Angiographically, the majority of these patients had triple vessel coronary artery disease and all had abnormal left ventricular contractile patterns The findings in these 15 patients contrast sharply with the 85 patients (Group IA and IB) who demonstrated a "normal" response to an extrasystole Only two had a history of congestive failure and only seven had radiologic evidence of cardiomegaly Less than half had evidence of a transmural myocardial infarction In these 85 patients angiography demonstrated that less than half had triple vessel disease and two thirds had an abnormal left ventricular contractile pattern

The hemodynamic findings (Figs 4 to 7) clearly separated patients in groups IA and IB from those in group IIA and IIB and are probably the basis for the differences observed in the postextrasystolic beat The patients in groups IIA and IIB were characterized by abnormally low cardiac outputs, stroke volumes and ejection fractions In addition, 60 per cent had increased end diastolic volumes as well This contrasts with the patients in groups IA and IB Here the majority had normal cardiac outputs storke volumes end diastolic volumes and ejection fractions

The factors which determine aortic systolic pressure include stroke volume and aortic impedance The interplay of these two factors probably determines as well the variable aortic systolic pressure response after an extrasystole, noted in the present study It is well known that the postextrasystole beat may demonstrate evidence of increased myocardial contractility[7] This response to an extra systole has been termed postextrasystolic potentiation It has been observed that the magnitude of potentiation after an extrasystole is directly dependent on the coupling interval and subsequent lengthening of the compensatory pause[8] Our failure to demonstrate a change in the response of the postextrasystolic beat with alterations of the coupling index in five patients in group IA and IB suggests the postextrasystolic potentiation may not be playing a critical role in determining systolic pressure in the postextrasystolic beat Katz[9] in a review of postextrasystolic potentiation, presented several examples (Figs 9 and 16 in ref 9) of no increase in systolic pressure in the postextrasystolic beat and ascribed this to the absence of any potentiation In the one patient tested in group IIA the coupling index was found to be a

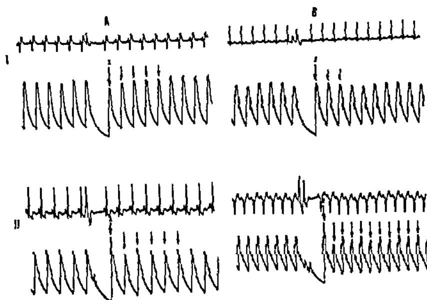


Fig 8 Aortic pressure–pulse response after an extrasystole taken at a slow paper speed to demonstrate the four responses observed Arrow (*X*) is the postextrasystolic beat whereas *the small arrows* are subsequent beats IA and IB are similar to *Fig 1* and IIA and IIB are similar to *Fig 2*

factor in determining the increase in systolic pressure in the postextrasystolic beat suggesting that such a response may be partly dependent on postextrasystolic potentiation It has previously been shown that potentiation is more readily demonstrated in the presence of myocardial dysfunction and not easily discernible in the non failing heart [8] We previously observed that the increase in stroke volume of the postextrasystolic beat was significantly greater in patients with impaired left ventricular function than in patients with normal left ventricular function Therefore the patients in groups IIA and IIB all of whom had the greatest impairment in left ventricular function probably had a significantly greater increase in stroke volume in the postextrasystolic beat than did patients in groups IA and IB Thus the changes in stroke volume present in the postextrasystolic beat may in part explain the distinct difference in the level of the systolic pressure attained *after the extrasystole*

The interplay of aortic run off and aortic impedance may further contribute to the systolic pressure level attained in the postextrasystolic beat During the compensatory pause after the extrasystole increased run off occurs as reflected by a progressive decrease in aortic diastolic pressure As a result of this fall in aortic pressure the aortic wall stiffness will decrease resulting in an over all decrease in aortic impedance Thus the increase in stroke volume associated with postextrasystolic potentiation will normally be counter balanced by a decrease in aortic impendance

The difference in response noted in patients in group IA and IB may be explained on the degree of responsiveness of aortic impedance Aortic arch and carotid baroreceptors also influence aortic impendance as a result of the decrease in aortic pressure during the compensatory pause [1,12] Under such circumstances one would anticipate increased impedance In the patients in group II the response of the vascular bed to the compensatory pause is probably different than in patients in group I The decreased cardiac output and stroke volume in group II is probably associated with a higher peripheral vascular resistance than in group I patients in whom both the mean cardiac output and stroke volume were normal (Figs 4 and 5) Therefore the increased aortic impedance already present in the patients in group II and the reported increased stiffness of the vascular walls and lack of response to vasodilatory stimuli present in such patients [13] would tend to maintain a high level of aortic impedance during the compensatory pause Under these conditions an increase in the stroke volume in the postextrasystolic beat could result in the observed increased systolic pressure in group II patients Finally it has been observed that augmentation of contractility, as a result of postextrasystolic potentiation is enhanced in the presence of increased aortic impedance [8] This

enhanced contractility would further increase the stroke volume in the postextrasystolic beat of the patients in group II

The different responses (Fig 8) after an extra systole are best explained by the variations in each group of postextrasystolic potentiation and decreased aortic impedance The differences in response between group I and group II patients clearly separate two distinct hemodynamic groups It is thus evident that the distinctive characteristic of the aortic pressure-pulse after an extrasystole may be clinically useful in suggesting the presence of significant left ventricular dysfunction Such an approach has been found useful in our non invasive section, and will be reported separately Furthermore, with increasing use of arterial cannulation and right heart pressure monitoring during acute myocardial infarction the response to an induced extra systole may be useful in defining the need for inotropic or reduced afterloading measures

Summary

The response of the aortic systolic pressure after an extrasystole was evaluated in 100 consecutive patients with coronary artery disease The patients were divided into four groups depending on the response of the first postextrasystolic beat Group IA (45 patients) had lower systolic pressure whereas group IB (40 patients) had a similar systolic pressure in the postextrasystolic beat as compared to beats preceding the extra systole Group IIA (12 patients) and group IIB (3 patients) demonstrated an increased systolic pressure in the first postextrasystolic beat with subsequent beats in group IIB also demonstrating pulsus alternans Congestive heart failure and cardiomegaly were significantly more frequent in group II as compared to group I patients In group IIA and IIB triple vessel disease was present in 83 and 100 per cent respectively as compared to 44 per cent in group I patients Left ventricular end diastolic pressure (mm Hg) was 14 ± 6 and 12 ± 7 in group IA and IB respectively as compared to 19 ± 9 ($p < 0.025$) in group IIA and 31 in group IIB Comparing groups IA and IB with each other for cardiac output stroke volume end diastolic volume and ejection fraction revealed no significant difference The cardiac output (L/min/M²) was 2.2 ± 0.6 for group IIA as compared ($p < 0.01$) to 2.8 ± 0.5 and 2.9 ± 0.5 in groups IA and IB Stroke volume (ml/M²) and ejection fraction were 30 ± 10 and 0.30 ± 0.08 respectively, for group IIA, which is significantly less as compared to group I patients The end diastolic volume (ml/M) in group IIA was 102 ± 28 which is significantly ($p < 0.001$) higher as compared to group IA and IB All patients in group IIB had an abnormal cardiac output end diastolic volume and ejection fraction Thus the differences in response between group I and group II patients to an extrasystole clearly define two distinct hemodynamic groups The responses observed to an extrasystole are best explained by variable response of each group to postextrasystolic potentiation and aortic impedance

The authors would like to thank Dr Irwin Hoffman for his critical review of this manuscript and the assistance in preparing this manuscript given by Brenda Hamby

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Peripheral hemodynamics in anephric patients with hypertension

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Anephric patients undergoing chronic hemodialysis therapy are anemic, may have hypertension, and are found to have a high cardiac index.[1,2] Neff and colleagues have shown that the high cardiac index is not responsible for the hypertension since restoration of the cardiac index to normal by blood transfusion raises rather than lowers the arterial blood pressure. Since these workers showed that hypertension in this clinical setting is related to an inappropriate level of systemic vascular resistance relative to the cardiac output, the present study of peripheral hemodynamics in anephric patients with hypertension was undertaken to see how they differ from normal.

Methods

Subjects. Four patients of mean age 32 years (range 21 to 44 years) who were anemic and hypertensive were studied 6 to 12 months following bilateral nephrectomy. Blood samples were drawn for plasma renin determinations 1 to 2 weeks after bilateral nephrectomy and renin was absent from the mixed venous blood. They were free from any significant complicating generalized systemic disease. All medications were withdrawn at least 7 days prior to the study. All four patients had arteriovenous shunts in position allowing vascular access for hemodialysis and were studied in the 24 hour period after dialysis when they were judged to be in optimal fluid and electrolyte balance. In the results described, data collected in limbs with an A-V shunt were excluded since it was found that the presence of the shunt distorted vascular measurements made in that limb. None had clinically detectable edema or evidence of congestive heart failure at the time of study. The patients remained hypertensive despite the absence of edema and progressive ultrafiltration hemodialysis to attain "dry weight."

Ten staff members of mean age 34 years (range 18 to 51 years) acted as controls. They had normal blood pressure and underwent the same peripheral vascular studies as the anephric, hypertensive patients described above.

I. Systemic measurements. In four anephric hypertensive patients cardiac output was determined under standard laboratory conditions by an indicator dilution technique using indocyanine green. Arterial blood pressure was measured with a Statham strain gauge transducer; plasma renin activity was measured by the method of Boucher. Total blood volume, red blood cell mass, and plasma volume were determined following injection of labelled serum albumen.

II. Peripheral vascular studies. Peripheral vascular studies were performed with the patients

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This study was supported in part by Contract No. PH-43 68-1333, Myocardial Infarction Research Program, National Institutes of Health.

Received for publication June 22, 1977.

Accepted for publication Sept. 30, 1977.

Reprint requests: Publication Office, Department of Cardiology, Cedars-Sinai Medical Center, 6 00 Beverly Blvd., Los Angeles, Calif. 90048.

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The different responses (Fig 8) after an extrasystole are best explained by the variations in each group of postextrasystolic potentiation and decreased aortic impedance The differences in response between group I and group II patients clearly separate two distinct hemodynamic groups It is thus evident that the distinctive characteristic of the aortic pressure-pulse after an extrasystole may be clinically useful in suggesting the presence of significant left ventricular dysfunction Such an approach has been found useful in our non invasive section, and will be reported separately Furthermore, with increasing use of arterial cannulation and right heart pressure monitoring during acute myocardial infarction, the response to an induced extrasystole may be useful in defining the need for inotropic or reduced afterloading measures

Summary

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Table II Forearm hemodynamics in 4 patients with anephric hypertension and 10 normal subjects

Measurement	*Anephric hypertension*	*Normal*	*P*
Forearm blood flow (ml./100 c c /min)	7 12 ± 1 65	3 66 ± 0 31	<0 05
Forearm vascular resistance (mm Hg/ ml./100 c.c./min)	23 5 ± 1 6	28 4 ± 3.5	NS
Forearm venous capacitance	3 95 ± 0 13	3.97 ± 0.29	NS

Mean ± SEM
NS = not significant

largest digital pulsation amplitude measured was accepted as the reading Skin temperatures of the digits were measured using 24 channel temperature measurements by tape application of a thermal probe

Digital blood flows, pulsation amplitudes and skin temperatures were all recorded at rest and after the use of a standard vasocilator technique which consists of having the patient ingest 30 c c of 43 per cent ethanol. At the same time the patient was surrounded by an electric blanket to produce body heating and the limbs were subjected to 5 minutes of reactive hyperemia as described above Readings were taken approximately 30 minutes after these interventions

The difference in the data obtained from normal subjects and anephric patients with hypertension was evaluated statistically by the Student s t test

Results

I Systemic hemodynamics In all four patients hypertension was present (Table I) Postoperatively in two patients there was no circulating renin activity while in two patients levels of 25 to 38 ng /100 ml /3 hours were found When these determinations were repeated no circulating activity was detected All four patients were anemic (hemoglobin—5 6 to 7 0 Gm /100 ml) In the three patients in whom cardiac index was measured the range varied from 4 11 to 5 32 L /min /M ^{2} while systemic vascular resistance varied from 1 015 to 1 510 units

II Peripheral Hemodynamics

(1) Forearm blood flow vascular resistance and venous capacitance Mean forearm blood flow in patients with anephric hypertension was 7 12 ml /100 c c /minute which was significantly higher than that of 3 66 ml /100/c c /minute found in normal control subjects (Table II) Mean forearm vascular resistance of 23 5 mm Hg/ml /100/c c /minute found in anephric hypertensives was not significantly different from than of 28 4 mm Hg/ml /100 c c /minute found in normal control subjects Mean forearm venous capacitance was almost identical in both groups being 3 97 c c /100 c c in normal subjects and 3 95 c c /100 c c in the anephric hypertensive group

Table III Oscillometric findings in 4 patients with anephric hypertension and 10 normal subjects

Measurement	*Anephric hypertension*	*Normal*	*P*
Above elbow (c c.)	0 96 ± 0 07	0 45 ± 0 02	< 0 05
Wrist (c c)	0.26 ± 0 03	0.26 ± 0 01	NS
Finger (mm)			
Before vasodilation	1 00 ± 0 [illegible]0	2 02 ± 0 34	< 0 05
After vasodilation	3 81 ± 0 68	4.57 ± 0 38	NS
Above knee (c.c)	1.23 ± 0 08	0 84 ± 0 05	< 0 01
Below knee (c c)	1 16 ± 0 07	0 83 ± 0 08	< 0 01
Ankle (c c)	0 35 ± 0 03	0 37 ± 0 01	NS
Toe (mm)			
Before vasodilation	0 96 ± 0 11	1 00 ± 0 11	NS
After vasodilation	2.13 ± 0 36	4 77 ± 0 51	< 0 05

Mean ± SEM
NS = not significant

(2) Oscillometry Mean pulsation amplitude of 0 96 c c above the elbow was significantly higher in patients with anephric hypertension than that of 0 45 c c in normal subjects ($p < 0.05$) Pulsation amplitudes at the wrist were identical in both groups (Table III) Mean finger pulsation amplitude before vasodilation was 1 00 mm ^{3} in anephric patients and this was less ($p < 0.05$) than 2 02 mm ^{3} found in normal subjects After standard vasodilation finger pulsation amplitudes were similar in the two groups

The pattern of findings of the upper limbs were nearly repeated in the lower limbs in that the mean pulsation amplitudes above and below the knee were 1 23 c c and 1 18 c c respectively in anephric hypertension This was significantly higher ($p < 0.01$) than the values of 0 84 and 0 83 c c found in normal subjects Pulsation amplitudes when measured at the ankle were similar to both groups of patients (Table III) When oscillometry was performed on the toes no significant differences between the two groups were found before vasodilation After vasodilation the pulsa

Table I Characteristics of patients with anephric hypertension

Patient	Sex	Age	Reason for nephrectomy	Blood pressure (mm Hg)	Hemoglobin (Gm / 100 ml)	Hematocrit (Gm / 100 ml)	Cardiac index L /min /M²	Systemic vascular resistance (units)	Preoperative renin (µg/ 100 ml)	Postoperative renin (ng /100 ml /3 hours)
S W	F	21	Transplantation	230/100	6 1	23	4 81	1 105	–	0·25
W H	M	22	Malignant hypertension	180/120	6 0	15	–	–	8 470	0
F A	M	35	Transplantation	170/100	5 6	13	4 11	1 510	–	0·38
E C	M	44	Transplantation	160/105	7 0	20	5 32	1 015	500	0

postcibal and supine in a quiet room at 68° F using a pneumatic plethysmograph After resting for 20 minutes oscillometry was performed above the elbow at the wrist, the upper thigh, above and below the knee, and at the ankle The greatest pulsation amplitude in a given area was compared to that produced by a 1 c c standard injection of air into the cuff The accepted reading was the greatest pulsation amplitude in a given area upon 10 mm Hg decrements of arterial blood pressure determined by sphygomomanometer Observations were not made in the limb in which the arteriovenous shunt was present since measurements made in such a limb were distorted by the presence of the shunt Venous occlusion plethysmography was used for the measurement of limb blood flow and venous capacitance The plethysmographic cuff was placed around the mid limb to measure limb blood flow, the second cuff connected to a cylinder of compressed air which was placed around the arm just above the elbow which allowed immediate pressure increase by sudden inflation of 30 mm Hg Forearm blood flow was calculated from the change in mean circumference during venous occlusion expressed in ml /100 c c of tissue/minute During the recording blood flow to the hand was occluded by the use of a third cuff inflated to supra systolic levels of pressure Venous capacitance was determined by an equilibration method described by Mason and Braunwald [3] During these measurements the forearm was elevated above the level of the heart Repeated determinations of limb blood flow and venous capacitance were undertaken to insure a relatively steady state When a steady state was considered to be present three successive measurements of limb flow and venous capacitance were undertaken averaged and utilized as the true measurement

Vascular resistance was defined as the mean arterial blood pressure measured in the arm by the auscultatory method divided by the forearm blood flow Mean arterial blood pressure was calculated by using the formula mean arterial pressure = diastolic blood pressure + ⅓ (systolic – diastolic blood pressure)

The reactive hyperemia response was determined in the forearm after release of 1 and 10 minutes of atrerial occlusion Following restoration of the circulation to the ischemic limb blood flow determinations were made at 5 15 30 60 and 90 seconds after one minute of arterial occlusion The test was then repeated occluding circulation to the limb for a period of 10 minutes and forearm blood flow was measured 5 15 30 60 90, 120 180 240 and 300 seconds after release

Forearm active hyperemia was determined by having the patient open and close a hand grip of 30 pounds tension once a second for 30 seconds Upon completion of this exercise circulation to the hand was once more occluded by supra systolic blood pressures and forearm blood flow was measured as described above This results described in the above active and reactive hyperemia reactions are the average of two measurements

Digital blood flow was measured in a similar fashion using a specially designed recording cuff sealed with plethysmographic sealing compound The digits used were the index finger and the second toe Venous occlusion was achieved by a 30 mm Hg cuff pressure applied at the wrist and ankle Calibrations were performed by injecting 0 01 ml of air into the system Vascular resistance was calculated as the ratio of mean arterial blood pressure to digital blood flow Oscillometric evaluation of digital pulsations was performed with digital cups in positions described above the

Table II Forearm hemodynamics in 4 patients *with anephric* hypertension and 10 *normal* subjects

Measurement	*Anephric hypertension*	*Normal*	*P*
Forearm blood flow (ml /100 c c /min)	7 12 ± 1 65	3 66 ± 0 31	<0 05
Forearm vascular resistance (mm Hg/ ml./100 c c /min)	23 5 ± 1 6	28 4 ± 3 5	NS
Forearm venous capacitance	3 95 ± 0 13	3 97 ± 0 29	NS

Mean ± SEM
NS = not significant

Table III Oscillometric findings in 4 patients with anephric hypertension and 10 normal subjects

Measurement	*Anephric hypertension*	*Normal*	*P*
Above elbow (c c)	0.96 ± 0 07	0 45 ± 0 02	< 0 05
Wrist (c c.)	0 26 ± 0 03	0 26 ± 0 01	NS
Finger (mm³)			
Before vasodilation	1 00 ± 0 20	2 02 ± 0 34	< 0 05
After vasodilation	3 81 ± 0 68	4.57 ± 0 38	NS
Above knee (c.c)	1.23 ± 0 08	0 84 ± 0 05	< 0 01
Below knee (c c)	1 18 ± 0 07	0 83 ± 0 08	< 0 01
Ankle (c c)	0.35 ± 0 03	0 37 ± 0 01	NS
Toe (mm)			
Before vasodilation	0 96 ± 0 11	1 00 ± 0 12	NS
After vasodilation	2 13 ± 0.36	4 7 ± 0.51	< 0 05

Mean ± SEM
NS = not significant

largest digital pulsation amplitude measured was accepted as the reading Skin temperatures of the digits were measured using 24 channel tempera ture measurements by tape application of a thermal probe

Digital blood flows pulsation amplitudes and skin temperatures were all recorded at rest and after the use of a standard vasodilator technique which consists of having the patient ingest 30 c c of 43 per cent ethanol At the same time the patient was surrounded by an electric blanket to produce body heating and the limbs were subjected to 5 minutes of reactive hyperemia as described above Readings were taken approxi mately 30 minutes after these interventions

The difference in the data obtained from normal subjects and anephric patients with hypertension was evaluated statistically by the Student s t test

Results

I Systemic hemodynamics In all four patients hypertension was present (Table I) Postoperatively in two patients there was no circulating renin activity while in two patients levels of 25 to 38 ng /100 ml /3 hours were found When these determinations were repeated no circulating activity was detected All four patients were anemic (hemoglobin–5 6 *to* 7 0 *Gm /100 ml)* In the three patients in whom cardiac index was measured *the range* varied from 4 11 *to* 5 32 L /min /M while systemic vascular resistance varied from 1 015 to 1 510 units

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(2) Oscillometry Mean *pulsation* amplitude of 0 96 c c above the elbow was significantly higher *in patients with anephric hypertension* than that of 0 45 c c in normal subjects ($p < 0.05$) Pulsa *tion amplitudes at the* wrist were identical in both groups (Table III) Mean *finger pulsation* ampli tude *before vasodilation* was 1 *00* mm³ in anephric patients and this was less ($p < 0.05$) than 2 *02 mm³ found* in normal subjects After standard vasodilation finger pulsation ampli tudes were similar in the two groups

The pattern of findings of the upper limbs were *nearly repeated in the* lower limbs in that the mean pulsation amplitudes above and *below the* knee were 1 23 c c and 1 18 c c respectively *in* anephric hypertension *This was significantly* higher ($p < 0.01$) than the values of 0 84 and 0 83 *c c found in normal subjects* Pulsation ampli tudes when *measured at the* ankle were *similar to* both groups of patients (Table III) When oscil lometry *was performed on the toes no* significant differences between the two groups were found before *vasodilation After* vasodilation the pulsa

Table IV Digital blood flow, vascular resistance, and temperature in 4 patients with anephric hypertension and 10 normal subjects

Measurement	*Anephric hypertension*	*Normal*	*P*
Finger blood flow (mm ³/sec)			
Before vasodilation	2 13 ± 0 42	0 97 ± 0 91	NS
After vasodilation	27 1 ± 9 5	14 7 ± 1 9	NS
Toe blood flow (mm /sec)			
Before vasodilation	0 89 ± 0 07	1 65 ± 0 05	<0 01
After vasodilation	6 12 ± 0 96	9 35 ± 0 91	<0 05
Finger resistance (mm Hg/mm ³/sec)			
Before vasodilation	74 ± 22	22 ± 2 4	<0 05
After vasodilation	4 88 ± 1 50	5 85 ± 1 15	NS
Toe resistance (mm Hg/mm ³/sec)			
Before vasodilation	150 ± 11	52 ± 3 7	<0 01
After vasodilation	24 ± 1 8	9 1 ± 2 4	<0 01
Finger temperature (° C)			
Before vasodilation	29 7 ± 0 7	29 7 ± 0 7	NS
After vasodilation	35 2 ± 0 5	35 9 ± 0 1	NS
Toe temperature (° C)			
Before vasodilation	25 9 ± 0 8	25 9 ± 0 8	NS
After vasodilation	31 7 ± 1 5	33 7 ± 0 4	NS

Mean ± SEM
NS = not significant

tion amplitude was 2 13 mm ³ in patients with anephric hypertension and 4 77 mm ³ in normal subjects (p < 0 05)

(3) Digital blood flow Mean finger blood flow in patients with anephric hypertension was not significantly different from that seen in normal subjects both before and after standard vasodilation (Table IV) Mean toe blood flow before vasodilation was 0 89 mm ³/sec in anephric patients and 1 65 mm ³/sec in normal subjects (p < 0 01) After vasodilation anephric patients had a mean toe blood flow of 6 12 mm ³/sec which was still significantly lower than the figure of 9 35 mm ³/sec (p < 0 05) observed in normal subjects

Mean vascular resistance in the finger before vasodilation was 74 mm Hg/mm ³/sec in anephric subjects, while in normal controls resistance was only 22 mm Hg/mm ³/sec (p < 0 05) (see Table IV) However, standard vasodilation abolished the difference between these groups Mean vascular resistance in the toe before vasodilation was significantly higher in anephric patients reaching a level of 150 mm Hg/mm ³/sec while in normals the figure was 52 mm Hg/mm ³/sec (p < 0 05) After vasodilation the anephric patient had a resistance of 24 mm Hg/mm ³/sec

Table V Comparison of minute resistance level produced by hyperemic methods in 4 patients with anephric hypertension and 10 normal subjects

Measurement	*Anephric hypertension*	*Normal*	*P*
10 minute reactive hyperemia			
Minimal resistance (mm Hg/ml /100 ml /min)	2 28 ± 0 39	1 75 ± 0 13	NS
30 lbs /30 sec active hyperemia			
Minimal resistance(mm Hg/ ml /100 ml /min)	3 25 ± 0 40	3 46 ± 0 58	NS
1 minute reactive hyperemia			
Minimal resistance (mm Hg/ml /100 ml /min)	3 36 ± 0 44	4 06 ± 0 38	NS

Mean ± SEM
NS = not significant

and in normal subjects resistance was 9 1 mm Hg/mm ³/sec (p < 0 01)

Mean finger and toe temperatures both before and after vasodilation were not significantly different between the two groups (Table IV)

(4) Reactive hyperemia Five seconds after release of the cuff in the one minute reactive hyperemia reaction mean forearm blood flow was 41 5 ml /100 c c /minute in patients with anephric hypertension This was significantly greater than the 20 4 ml /100 c c /minute recorded in normal control subjects (p < 0 001) (Fig 1) This increase in forearm blood flow was maintained at the 15 30 and 60 second post occlusion observation periods After 90 seconds however there was no significant difference between the two groups Five and 15 seconds after cuff release in the 10 minute reactive hyperemia reaction the forearm blood flow in anephric patients was 58 and 57 ml / 100 c c /minute However in the normal subjects the levels were 38 2 and 40 7 ml /100 c c /minute respectively (p < 0 01 and p < 0 0025) Thirty seconds after cuff release there was no significant difference between the two groups The values in the two groups remained essentially the same at the 60 90, 120 and 180 second periods of observation After 180 seconds the difference between the two groups became significant, being 7 84 ml /100 c c /minute in the hypertensive patients and 5 08 ml /100 c c /minute in the normal patients (p < 0 025) Increase in forearm blood flow in the

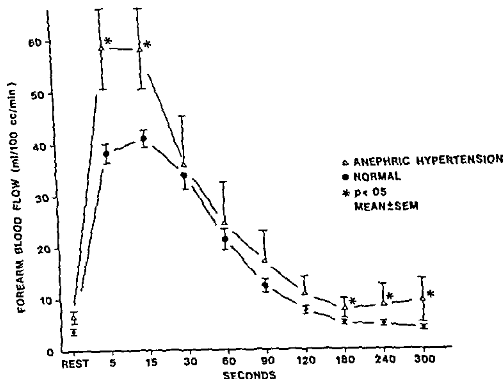


Fig 1 Mean 10 minute hyperemia reaction in 10 normal subjects and five patients with anephric hypertension Forearm blood flow at 5 and 15 seconds after cessation of circulatory arrest is greater in patients with anephric hypertension The increase seen in 180 to 300 seconds may reflect the greater resting forearm blood flow seen in anephric hypertension

anephric patients was maintained at both 240 and 300 second observation periods

In the one minute reactive hyperemia reaction a significant and marked increase in flow occurred in the anephric patients when compared to the normal subjects This increase in flow was seen at the 5 15 30 and 60 second periods of observation after cuff release (Fig 2)

(5) *Thirty second/thirty pound active hyperemia reaction* Five and 15 seconds after cuff release in this reaction no significant differences were found between the hypertensive and control groups However at 30 seconds after cuff release the blood flow in normal subjects which had reached its maximum 15 seconds started to fall and reached a level of 18 4 ml /100 c c /minute Conversely in the anephric patients the level of forearm blood flow continued to increase reaching a level of 39 6 ml /100 c c /minute which was significantly greater than that seen in normals ($p < 0\ 001$) Sixty seconds after cuff release mean forearm blood flow started to fall in anephric patients and reached a level of 28 8 ml /100 c c / minute This was still significantly greater than that of 15 2 ml /100 c c /minute in the normal controls ($p < 0\ 0025$) This increase in forearm blood flow was maintained at the 90 120 and 180 second observation periods and it was only at 240 seconds after cuff release that the difference between the two groups become insignificant (Fig 3)

Discussion

While essential hypertension is usually characterized by a normal cardiac output and increased systemic vascular resistance patients with hypertension associated with end stage renal failure appear to have a high cardiac output and normal or only slightly increased systemic vascular resistance This is similar to the hemodynamic pattern seen in young patients with labile essential hypertension[1 4 6] While bilateral nephrectomy has been found to be effective in many uremic patients with uncontrollable hypertension this is not always the case as is seen in the four patients included in this study[7 11] Thus

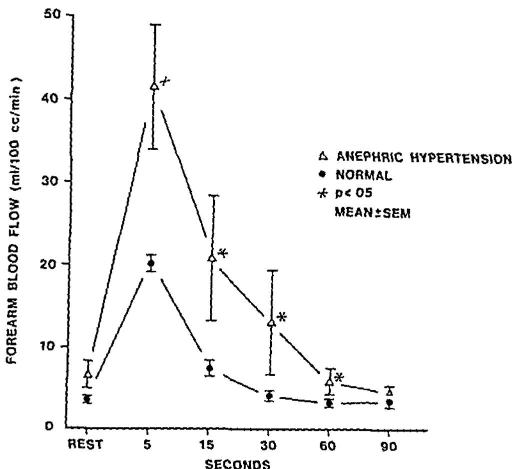


Fig 2 The mean 1 minute reactive hyperemia reaction in 10 normal subjects and five patients with anephric hypertension A marked increase in forearm blood flow is seen between 5 to 60 seconds after cessation of circulatory arrest

nearly all patients with high renin have their hypertension lowered by nephrectomy, fewer patients with low or normal renin uremic hypertension will respond

Anemia In contrast to young patients with essential hypertension anephric patients with hypertension are invariably anemic and their hematocrits rarely exceed 25 per cent Patients with severe anemia alone usually have an increased cardiac output at rest while their blood pressure is normal unless other complicating diseases are present[13] The systemic vascular resistance is correspondingly low An important factor here is the decreased viscosity of blood for even if the caliber of the vessels (i e their geometric factors) were normal the reduced viscosity would lead to lower resistance[12] Patients with anephric hypertension reported in this study and elsewhere[1] have a systemic vascular resistance that falls within the normal range, but for the degree of anemia and cardiac output present it is far too high[12 13]

While anemic patients with normal kidney and normal arterial blood pressure may be theoretically preferable as control subjects in such a study as this a survey of hospital population showed that few such patients exist except where complicated by other multiple disease processes

Anemia and forearm blood flow In 1909 Hewlett and Van Zwaluwenburet[14] reported that in patients with anemia comparable to that seen in the present study the anemia per se has no effect on the forearm blood flow Verel and Duff[15] also showed that when the level of hemoglobin exceeded 4 Gm /100 ml the limb blood flow was within the normal range It was only in subjects with hemoglobin values below 4 Gm /100 ml that the rate of blood flow was persistently increased These observations suggest that in anemia patients the oxygen demands in the limb are met initially by greater extraction of oxygen and that flow rates only increase when little further oxygen extraction is possible

When a plethysmograph is placed as high as possible in the forearm Grant and Pearson[16] observed that 85 per cent of the tissue enclosed is muscle and the remainder is bone and skin Since the degree of anemia observed in the present study has little effect upon resting muscle blood flow one can reason that the elevated resting

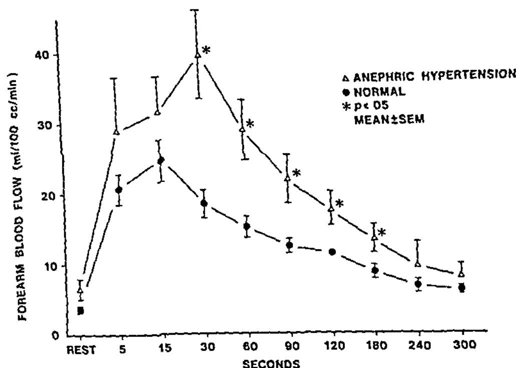


Fig 3 Mean 30 second/30 pound active hyperemia reaction in 10 normal subjects and five patients with anephric hypertension Th peak forearm blood flow is seen at 15 seconds in normal subjects that is delayed until 30 seconds in patients with anephric hypertension Thirty to 180 seconds after the release of the circulatory arrest the cessation of work by the limbs forearm blood flow is greater in patients with anephric hypertension.

forearm blood flow was in fact due to the hypertension This agrees with Abramson and Fierst [7] who found a greater limb blood flow in patients with hypertension as compared with normal subjects From these observations it would appear therefore that the vessels in skeletal muscle are less constricted than other vessels in the body so that at rest blood flow through the muscles is increased [1] The findings of normal resting limb vascular resistance agree with earlier findings of Stead and Kunkel

Anemia and venous tone While the needs of the organism are apparently served by maintaining right heart filling pressures through the mechanism of generalized increase in venous tone the compensatory response of the veins in patients with chronic anemia is usually not observed until the hemoglobin level is under 5 Gm /100 ml [9] The finding of normal venous tone in patients with anephric hypertension is in keeping with the finding in other patients with essential hypertension that the widespread arteriolar constriction is not associated with generalized constriction of veins [2]

Pulsatation amplitudes On oscillometric examination one sees increased pulsation amplitudes in the areas above the elbow and above and below the knee However more distally at the wrist and ankle there is no difference between the pulsation amplitude seen in patients with anephric hypertension and normal controls This increased proximal pulsation amplitude may be related to the degree of anemia present which often gives a clinical impression of a large pulsation amplitude which sometimes is said to be collapsing in character [22]

Pulsation amplitudes observed in the digits are somewhat paradoxical In the fingers of patients with anephric hypertension before vasodilation the mean pulsation amplitude was diminished (Table III) while after standard vasodilation pulsation amplitudes are similar to those seen in normal control subjects However pulsation amplitudes are normal in the toe before vasodilation After standard vasodilation one sees a diminished pulsation amplitude in the toe of patients with anephric hypertension Why vasodilatory stimuli can overcome the vasospasm present in the fingers in patients with anephric hypertension but are unable to do so in the toes

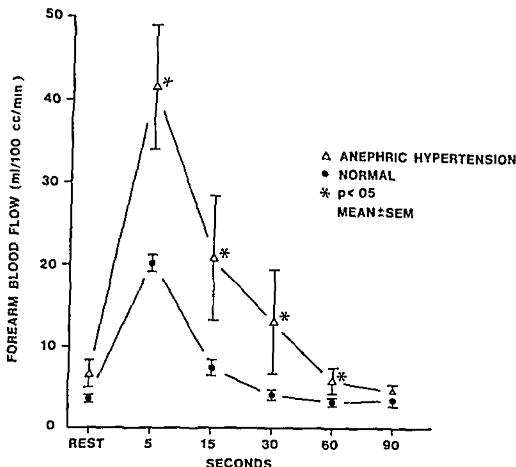


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whereas in the anephric hypertensive group forearm blood flow continues to increase creating a significant difference in the levels of flow At 60 seconds after cuff release the mean forearm blood flow starts to fall in anephric hypertensive patients but the increase in forearm blood flow is maintained at 90 120 and 180 seconds of observation Since Stead and Kunkel[19] and Abramson and Fierst[17] have obtained normal flows after reactive hyperemia in hypertension it would seem that one more possibly this as seen in patients with anephric hypertension may be influenced by the degree of anemia present which would tend to increase blood flow

In addition there may be other factors present influencing the results obtained in these patients The precise state of their sodium balance cannot be defined, and some degree of peripheral and autonomic nervopathy may be present All of these factors in varying degree could participate in alterations in hemodynamic control

Summary

Peripheral hemodynamics were examined in a group of four anephric patients with hypertension and the results were compared with a group of 10 normal subjects Measurements of systemic hemodynamics in these anephric patients showed increased arterial blood pressure and a modest increase in cardiac index Renin blood levels were negligible Mean forearm blood flow was significantly higher in the anephric patients This was probably a reflection of the increased arterial blood pressure since mean forearm vascular resistance was within normal limits Mean forearm venous capacitance was also within normal limits

Oscillometric examination showed markedly increased pulsation amplitudes proximally in the limbs of anephric patients while at the wrist elbow fingers and toes pulsation amplitudes were either normal or diminished

Skin blood flow as reflected in both fingers and toes was significantly diminished in anephric patients while skin temperature was normal While this may indicate normal capillary blood flow in anephric hypertension constriction at the precapillary network level as seen by the increased resistance occurring in the skin is present Changes in the 1 and 10 minute reactive hyperemia and 30 pound/30 second active hyperemia reactions showed that in anephric patients a greater time period of increased levels of flow was obtained in all three reactions

These data suggest that the difference seen between anephric and normal subjects in their peripheral vasculature in part result from the hypertension severe anemia and other factors which may be present

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requires further investigation The tendency for hypertensive ulcers to form on the lower limb may, in part, be a reflection of the inability of the pulsation amplitudes in the lower limbs to respond to vasodilatory stimuli such as reactive hyperemia heat, and alcohol ingestion [3] Inasmuch as hypertensive ulcers are usually of an ischemic nature, it is assumed either that the organic changes in the arterioles or small arteries produce an area of relatively poor arterial blood supply in which minor injury can initiate an ulcer or that occlusion of the arterioles or small arteries cause an area of infarction of the skin which breaks down to form an ischemic ulcer [4]

Digital blood flow Skin blood flow can be quantitated by the measurements of blood flow in the digits In patients with anephric hypertension one sees diminished skin blood flow before vasodilation in the toes, due, in part to markedly increased resistance in both sets of digits These findings of increased skin resistance and normal or diminished muscle resistance agree with the results of Brod[25] who found a similar state in the peripheral vasculature of patients suffering from essential hypertension After standard vasodilation one sees diminished resistance in the fingers in patients with anephric hypertension (Table IV) However, by contrast, a state of diminished blood flow and elevated resistance continues in the toe, indicating a difference in reactivity between upper and lower digits of uncertain cause

Skin blood flow is regulated through the vasomotor nerves in the interest of body temperature regulation [26, 27] The fact that under given environmental circumstances the blood flow through the skin is of the same order in normal subjects and in subjects with hypertension may mean no more than that the mechanism of the dissipation of heat from the body is the same in the two groups Stead and Kunkel[19] obtained similar blood flows through the hand at 43° C in normal subjects and in subjects with essential hypertension By contrast, in acute nephritis, hand blood flow after releasing sympathetic tone was larger in the phase of hypertension, while in pheochromocytoma it was smaller

Digital temperature Since digital temperature is a reflection of capillary blood flow the finding that both before and after vasodilation the skin temperature is essentially identical in both normal subjects and in patients with anephric hypertension may indicate that capillary blood flow is within normal limits in anephric hypertension [8] However, since digital blood flow is markedly reduced at rest, this tends to indicate excessive resistance at the pre capillary arteriolar level

Reactive hyperemia When the reactive hyperemia reactions are considered, the results are similar to that obtained in other types of hypertension Pickering [9] and Prinzmetal and Wilson[30] have shown that with circulatory arrest lasting up to 10 minutes the rate of blood flow increased to the same extent in subjects with benign essential hypertension, malignant hypertension, and chronic nephritis with hypertension as in subjects with normal arterial blood pressure This was confirmed by Conway,[31] who added patients with renal vascular disease and primary hyperaldosteronism In the present study, 5 and 15 seconds after the release of the cuff in the 10 minute reactive hyperemia reaction blood flow in the anephric hypertensive patients was greatly increased above normal This increase may reflect a need for greater blood flow because of anemia to repay the oxygen debt present in the limb The increase seen in this reaction at 180 seconds to 300 seconds of observation is probably a reflection of the higher resting forearm blood flow in anephric patients (Fig 1)

In the one minute hyperemia reaction an increase is seen in forearm blood flow at 5 15, 30 and 60 seconds of observation which may once more represent repayment of the oxygen debt and the need for greater blood flow to achieve this Conway[31] found that the average minimal resistance obtained during reactive hyperemia was greater in hypertensive patients than in normal subjects However this was not seen in the present study (Table V) where resistances in both the 10 minute reactive hyperemia 1 minute reactive hyperemia and 30 seconds reactive hyperemia responses are not significantly different from one another This difference may once more reflect the influence of anemia but it is an area in which further study is indicated

Active hyperemia When both groups of individuals were subjected to the 30 pound/30 second active hyperemia reaction there was no significant difference early after cuff release (Fig 3) However, at 30 seconds after cuff release the blood flow in the normal group which had reached the maximum at 15 seconds starts to fall

Effect of probucol in hyperlipidemic patients during two years of administration

William B Parsons Jr M D
Madison Wisc

Probucol a new cholesterol reducing agent is a bis phenol with a chemical structure unlike presently recognized lipid lowering drugs (Fig 1) It lowers serum cholesterol in mice rats dogs and monkeys without significantly affecting triglycerides[1-4] The drug has shown no adverse effects in animals with one notable exception an apparent species specific sensitization to epinephrine induced ventricular fibrillation in dogs[2]

In most hypercholesterolemic humans probucol has reduced serum cholesterol without important side effects or toxicity[7] Triglyceride levels have been unchanged [9] widely variable or somewhat reduced

The mechanism of probucol s cholesterol lowering action remains undetermined It has no effect on incorporation of mevalonate into cholesterol Cyclic precursors of cholesterol (desmosterol and 7 dehydrocholesterol) do not accumulate in serum of animals or man[3] Studies on incorporation of acetate *in vivo* (rats mice) and *in vitro* (rat liver slices) gave inconclusive results One study which used larger than usual doses (2 0 Gm per day) in patients with familial hypercholesterolemia showed reduction of cholesterol synthesis increased fecal excretion of bile acids and reduced intestinal absorption of lipids

In the present clinical study ambulatory outpatients with several types of hyperlipoproteinemia received probucol for two years without accompanying dietary alteration

From th J ckson Clinic and F und t n M dison Wisc
Recei ed f public t on Aug 3, 1977
Accepted f p bl t on Sept 19 1977
Reprint req ests William B Parso s, J M D 7331 E O born Dri e (Suit 205) Scottsdal Ariz. 85_51

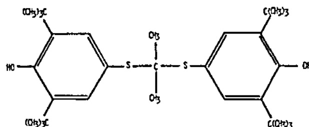


Fig 1 Structural formula for 4 4 [isopropylidenethio] bis(2 6-di t butylphenol] probucol (DH 581)

Subjects and methods

The subjects of this study participating with informed consent were 31 men and 31 women ages 32 to 66 years (mean 55 years) whose serum cholesterol levels exceeded 255 mg /100 ml before treatment All were ambulatory outpatients from the author s private practice None had received lipid lowering drugs in the preceding 60 days The participants were instructed to eat their usual unrestricted diets but to avoid gaining weight

During a baseline period of placebo administration three blood samples were drawn at weekly intervals for lipid determinations Probucol was then administered orally in doses of 500 mg (two tablets) twice daily Subsequent cholesterol and triglyceride determinations were performed after two weeks four weeks and then at four week intervals always after an overnight fast

After one year of probucol administration 11 subjects were removed from the study and given other medication because their mean serum cholesterol levels had been reduced by less than 10 per cent from baseline values One other

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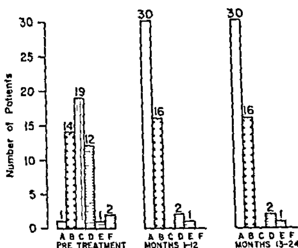


Fig 2 Effect of probucol in 43 hyperlipidemic individuals during two years of administration Code (mean serum cholesterol levels, mg/100 ml) A = 250 or less B = 251 2,5 C = 2 6-300 D = 301-350 E = 351-400 F = 401 or higher

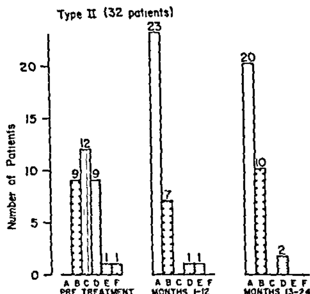


Fig 3A Effect of probucol in 32 patients with Type II hyperlipoproteinemia (HL) Code for mean serum cholesterol levels same as in *Fig 2*

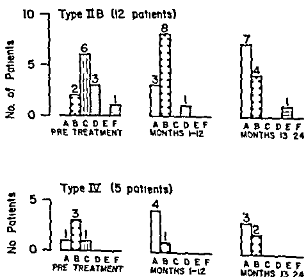


Fig 3B and C *B* Effect of probucol in 12 patients with Type IIB HL Code for mean serum cholesterol levels same as in *Fig 2* *C (lower)* Effect of probucol in five patients with Type IV HL Code for mean serum cholesterol levels same as in *Fig 2*

or less in both years of treatment compared to six of 17 (35 per cent) of these individuals at base line

Triglyceride levels Mean serum triglyceride levels for HL types characterized by hyperglyceridemia (IIB IV V) were lower during probucol administration but reduction of these lipids in individuals was inconsistent and quite variable

Side effects Three patients complained of anal pruritus which did not prevent continuation of therapy One patient had mild diarrhea and another reported softer than usual stools without diarrhea both improved while continuing medication Three patients had irritable bowel symptoms (gas bloating abdominal distress) which persisted in two of them despite substitution of placebo tablets

Toxicity No abnormalities attributed to probucol were noted in tests of hepatic renal or hemopoietic function No drug related effects occurred in associated diseases including coronary disease diabetes hypertension and gout

Comment

The patients in this study showed reduction in their elevated serum cholesterol levels notably in Types II and IIB HI but in other types also without dietary restriction No serious side effects or toxicity occurred confirming other reports of few if any symptoms or adverse effects related to probucol None of the reported clinical trials have revealed any reactions in humans like the species specific sensitization to epinephrine induced ventricular fibrillation in dogs[2,3] Polachek and associates[1] unfortunately were not able to obtain appropriate studies to exclude paroxysmal arrhythmia during hospitalization in their patient who had experienced dizziness and palpitation after each of three 500 mg doses in the first few days of therapy They attributed this reac

Table I Changes in mean serum cholesterol levels (±S E) during first year of probucol therapy

HL type	No	Baseline average 3 values	Months of therapy ¼	1	2	3	4	5	6	7	8	9	10	11	12
II	32	298 ±7	245 ±8	240 ±7	240 ±7	252 ±8	237 ±8	241 ±7	236 ±6	236 ±6	235 ±6	239 ±6	244 ±5	234 ±6	237 ±5
IIB	12	305 ±11	262 ±15	259 ±13	246 ±15	256 ±15	260 ±14	253 ±17	254 ±10	249 ±12	237 ±13	244 ±9	247 ±13	246 ±13	257 ±1[illegible]
IV	5	265 ±5	239 ±25	225 ±20	214 ±19	222 ±17	228 ±14	226 ±14	228 ±17	220 ±20	215 ±11	240 ±16	232 ±19	228 ±14	233 ±15
V	1	409	378	340	384	346	290	280	392	328	266	254	384	304	23[illegible]

Table II Changes in mean serum cholesterol levels (±S E) by six month periods

HL type	No	Baseline average 3 values	1 6 months	7 12 months	13 18 months	19 24 months
II	32	298 ±7	242 ±6	238 ±5	244 ±8	239 ±7
IIB	12	305 ±11	256 ±12	247 ±11	247 ±15	248 ±13
IV	5	265 ±5	226 ±16	228 ±14	225 ±15	230 ±19
V	1	409	344	339	275	285

Table III Changes in mean serum triglycerides (±S E) by six month periods in HL Types IIB IV and V

HL type	No	Baseline average 3 values	1 6 months	7 12 months	13 18 months	19 24 months
IIB	12	223 ±17	213 ±23	198 ±22	180 ±21	191 ±19
IV	5	427 ±42	414 ±78	477 ±102	361 ±72	409 ±83
V	1	1 227	1 151	654	609	792

patient left the study after one year for personal reasons Probucol therapy continued for a second year in the remaining 50 patients, whose results are the subject of this report

Cholesterol was measured by the N 24 Auto Analyzer method in which isopropanol extraction precedes the automated determination [16] Triglycerides were determined by a modification of the Lofland method [17] After paper electrophoresis by the method of Lees and Hatch,[18] patterns of hyperlipoproteinemia (HL) were categorized by the Fredrickson Lees Levy classification [19]

Results

Cholesterol levels Probucol administration resulted in prompt and sustained reduction of mean serum cholesterol levels in patients with Type II HL (32 patients), Type IIB HL (12 patients), Type IV HL (five patients), and Type V HL (one patient) as shown in Tables I and II In every group the mean reduction after two weeks approached but did not equal that at subsequent intervals The first year s mean reductions were sustained through the second year of probucol therapy without evidence of escape (Table II)

In HL Types II and IIB the mean cholesterol values for each six month period of treatment (Table II) were significantly lower than for the baseline period ($p = < 01$) Differences between mean values at baseline and after two weeks were also significant in these groups ($p = < 05$) Reductions in Types IV and V HL showed similar trends which in smaller numbers of participants failed to achieve statistical significance

Fig 2 shows the distribution of average serum cholesterol levels in individuals at baseline (three values) and throughout each of two years of probucol therapy omitting the one patient with Type V HL Thirty of 49 (61 per cent) in the first year and 31 of 49 (63 per cent) in the second year had mean cholesterol levels of 250 mg /100 ml or less Only 6 per cent (three of 49) had mean levels higher than 300 mg /100 ml in each year of therapy compared to 31 per cent (15 of 49) at baseline

Fig 3 depicts individual results in HL Types II IIB and IV Probucol reduced the average cholesterol level in Type II HL to 250 mg /100 ml or less in 23 of 32 (63 per cent) in the second year All five patients with type IV HL and 11 of 12 with Type IIB HL (94 per cent of these two groups combined) had average levels of 275 mg /100 ml

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tion which necessitated withdrawal of the drug, to hypersensitivity

The ultimate goal of lipid reduction is to lessen the incidence of atherosclerotic disease and its serious often fatal complications Conclusive evidence of such benefit is difficult to demon strate even in long term clinical trials involving large numbers of participants Like most of the established lipid lowering drugs, probucol has reduced experimental atheromas in animals [4] Also like older drugs in this category, its ability to prevent or retard atherosclerosis has not been established

In the absence of definite guidelines from field trials, the decision to treat or not to treat hyper lipidemia will continue to depend on clinical judgment Clinicians should welcome the avail ability of probucol, a new and distinctive choles terol reducing agent with convenient twice daily oral dosage and virtual freedom from side effects or adverse reactions The drug appears to be most effective in Type II and Type IIB HL but it can reduce cholesterol levels in other groups Its inconsistent activity regarding triglyceride levels is not an important drawback, inasmuch as these lipids are most amenable to reduction by appro priate diet which is generally recommended as the first measure in a regimen for hyperlipidemia Other investigators have demonstrated an addi tive effect on cholesterol levels by combining probucol therapy with dietary modification [1 14]

Further studies are needed to delineate probu col s effect in familial Type II HL both as a single agent and in combination with diet and other drugs (cholestyramine niacin) presently recom mended for this syndrome with a high incidence of premature myocardial infarction and sudden death [6] Because its mechanism of action is likely to differ from drugs currently used for this disor der, probucol may improve the success of combi nation therapy in familial Type II HL in which hypercholesterolemia is often resistant to treat ment

Summary

Probucol a new cholesterol lowering agent was administered to ambulatory outpatients representing several classes of hyperlipoprotein emia (HL) for two years without dietary restric tion In 32 patients with Type II HL and 12 with Type IIB HL, statistically significant reduction in mean serum cholesterol levels occurred within two weeks and persisted throughout two years of therapy at constant dosage (500 mg twice daily) In smaller numbers of patients with Type IV HL (five patients) and Type V HL, (one patient) similar trends in mean serum cholesterol were observed but failed to achieve statistical signifi cance Mean triglyceride levels were generally lower during probucol therapy but varied widely between individuals The drug was well tolerated with no toxicity and few side effects (mild diar rhea, gas bloating anal pruritus) Probucol should be a valuable addition to the therapeutic armamentarium for hypercholesterolemia

James T Lowe Ph D and Harold L Taylor Ph D of The Dow Chemical Company Indianapolis Indiana generously furnished supplies of probucol for this study Richard A Stein Ph D (Armour Research Center Scottsdale Arizona) performed the statistical analyses The author gratefully acknowledges these important contributions

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Antihypertensive effect of cardiovascular Ca^{2+}-antagonist in hypertensive patients in the absence and presence of beta-adrenergic blockade

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Altered cardiac and vascular smooth muscle functions are considered major contributing factors in the development of hypertension Muscle functions are controlled, at least in part by the intracellular ionic environment, especially the distribution of Ca in the cell It is known that Ca^{2} is regulated by cell membranes and sarcoplasmic reticulum Recently it has been reported that in spontaneously hypertensive rats (Okamoto Aoki hypertensive strain SHR) the ability of the vascular smooth muscle membrane to retain Ca and the ATP dependent Ca uptake sarcoplasmic reticulum are reduced [1-7] Also, decreased vascular smooth muscle relaxation[8] may lead to hypertension These findings suggest that abnormalities of Ca^{2} flux through cell membranes Ca^{2} uptake and release by sarcoplasmic reticulum in the cardiovascular muscle cells may play a role in the development and persistence of hypertension

Calcium antagonists inhibit influx and release of calcium from sarcoplasmic reticulum They antagonize the Ca ion function responsible for excitation and contraction in the electromechanical coupling thus blocking contraction of myocardial and vascular fibers and inducing their relaxation This has a negative inotropic effect on the myocardium and a vasodilatation result[9-11] These actions, reduction of myocardial contraction and vasodilatation can be expected to lower elevated blood pressure Therefore Ca antagonists are of interest in the management of hypertension [1]

Nifedipine, a Ca antagonist with distinct coronary vasodilating properties was studied in normotensive volunteers and in hypertensive patients as to its hypotensive action, its cardiovascular effects and its influence on plasma renin Changes of heart rate and plasma renin activity induced by nifedipine and the effect of beta blockade (propranolol) were measured to examine the significance of a combined administration Also the mechanism of action of nifedipine in the control of the vascular system is discussed in comparison with that of other Ca^{2} antagonists such as verapamil [13-14]

From the Second Department of Medicine Nagoya City University School of Medicine Nagoya Japan

Received for publication Aug 19 19
Accepted for publication Nov 21 19

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Materials and method

Four normotensive healthy male volunteers (Table I) aged 34 to 45 years (38 5 ± 5 4 years) (mean ± SD) and 24 hypertensive patients (10 hospitalized and 14 outpatients) participated in this study The patients consisted of 16 males

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Table I Effects of Ca² antagonist (nifedipine) and beta blockade (propranolol) on blood pressure heart rate and PRA* in normotensive group

Treatment		Nifedipine 10 mg						Nifedipine 30 mg						Nifedipine 30 mg and Propranolol 0.2 mg /Kg body wt					
		Blood pressure (mm Hg)		Heart rate (beats/ min)		PRA (ng /ml /h)		Blood pressure (mm Hg)		Heart rate (beats/ min)		PRA (ng / ml /h)		Blood pressure (mm Hg)		Heart rate (beats/ min)		PRA (ng /mL/h)	
Case No†		B	1 hour	B	1 hour	B	1 hour	B	1 hour	B	1 hour	B	1 hour	B	1 hour	B	1 hour	B	1 hour
1	S	114	112	64	70	0 8	1 3	130	110	54	66	0 6	1 4	110	100	68	64	0 4	0 3
	D	72	68					80	70					64	60				
2	S	126	128	64	66	3 1	3 8	114	106	62	78	3 5	12 2	120	108	62	78	3 7	2 1
	D	80	72					60	64					76	68				
3	S	116	120	68	66	0 9	1 5	100	92	64	62	0 9	2 4	114	98	70	58	4 4	4.2
	D	80	82					64	60					72	68				
4	S	120	120	70	72	0	1 3	110	110	68	64	0 4	0 4	130	110	66	66	0 4	0 3
	D	80	76					70	70					80	70				
SM		119 0	120 0	66 5	68 5	1 25	1 98	113 5	104 5	62 0	67 5	1 35	4 10	118 5	104 0	66 5	66.5	2.23	1 73
± SD		5 3	6 5	3 0	3 0	1 2[illegible]	1 [illegible]	1[illegible]5	8 5	5 9	7 2	1 45	5 46	8 7	5 9	3 4	8 4	2.13	1.86
p value		> 0 1 ns		> 0 1 ns		< 0 02 s		> 0 1 ns		> 0 1 ns		> 0 1 ns		< 0 01 s		> 0 1 ns		> 0 1 ns	
DM		78 0	74 5					68 5	66 0					73 0	66 5				
± SD		4 0	6 0					8 7	4 9					6 8	4 4				
p value		> 0 1 ns						> 0 1 ns						< 0 05 s					
Average of paired % change of control value																			
SM			101		103		276		93		110		237		88		101		76
± SD			2		5		250		6		17		104		3		18		16
DM			96						97						91				
± SD			5						8						4				

*Abbreviations PRA = plasma renin activity B = before treatment 1 hour = 1 hour after treatment S = systolic blood pressure D = diastolic blood pressure M = mean value SD = standard deviation of the mean s = statistically significant ns = not statistically significant
†Case 1 = 41 years, male Case 2 = 34 years male Case 3 = 74 years male Case 4 = 45 years, male

and eight females mean age 45 9 ± 9 3 years (from 29 to 63 years) The average blood pressure was 119 0 ± 5 3 mm Hg (from 114 to 126 mm Hg) systolic and 78 0 ± 4 0 mm Hg (from 72 to 80 mm Hg) diastolic in the normotensive and 176 3 ± 23 8 mm Hg (from 150 to 240 mm Hg) systolic and 109 5 ± 15 1 mm Hg (from 90 to 150 mm Hg) diastolic in the hypertensive group Systolic blood pressure of 150 mm Hg or higher and diastolic blood pressure of 90 mm Hg or higher on at least three separate measurements in the hospital (Nagoya City University Second Department of Medicine) were criteria for admission to the trial

Blood pressure was measured on four different occasions at rest in the supine position Arterial blood pressure was measured by auscultation Heart rate was measured at the cardiac apex pulse rate or from a simultaneously recorded electrocardiogram The results are values averaging four readings

Ten hypertensive patients (Table II) were hospitalized at Nagoya City University Hospital They were selected from the total of 24 cases according to clinical history physical status measurements of routine urinalysis hematocrit white blood cell red blood cell serum glucose sodium potassium chloride bicarbonate calcium cholesterol protein creatinine clearance regitine test and rapid sequence intravenous pyelogram Their clinical diagnosis and findings are summarized in Table II They consisted of seven essential and three secondary hypertensive subjects (one female and 9 males) mean age 44 9 ± 10 7 years (from 29 to 63 years) Blood urea nitrogen 16 7 ± 6 7 mg /dl (7 to 27 mg /dl) $SV_1 + RV_5$ in electrocardiogram 4 87 ± 2 17 mV (2 1 to 9 4 mV) cardiothoracic ratio in chest

Antihypertensive effect of cardiovascular Ca^{2+}-antagonist in hypertensive patients in the absence and presence of beta-adrenergic blockade

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0002-8703/78/0296-0218$00 90/0 © 1978 The C

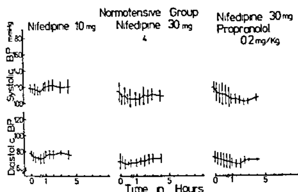


Fig 1 Changes of blood pressure with 10 and 30 mg of nifedipine (Ca antagonist) and combined administration of 30 mg of nifedipine and propranolol (beta blockade) in normotensive volunteers Values are mean ± standard deviation

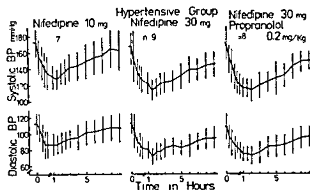


Fig 2 Hypotensive effect of 10 mg and 30 mg of nifedipine (Ca antagonist) and combined administration of 30 mg of nifedipine and propranolol (beta blockade) in hypertensive patients Values are mean ± standard deviation

pressure decreased significantly after 10 mg of nifedipine from 172 9 ± 17 1 to 130 3 ± 15 7 mm Hg ($p < 0\ 001$) in systolic and from 112 9 ± 13 8 to 86 6 ± 14 6 mm Hg ($p < 0\ 01$) in diastolic pressure (25 per cent and 23 per cent reduction respectively) (n = 7) After administration of 30 mg nifedipine blood pressure decreased somewhat more namely from 166 9 ± 17 6 to 122 0 ± 13 8 mm Hg ($p < 0\ 001$) or 27 per cent and 28 per cent reduction (n = 9) Combined administration of nifedipine and propranolol produced a 32 per cent decrease in systolic and a 30 per cent decrease in diastolic values one hour after medication (n = 8) (Table III and Fig 2)

Heart rate increase by nifedipine and its inhibition by propranolol Ten mg nifedipine slightly increased heart rates of normotensive patients from 66 5 to 68 5 beats/minute and with 30 mg it changed from 62 0 to 67 5 beats/minute one hour after medication Combined administration of nifedipine and propranolol induced no significant changes (Table I Fig 3) In hospitalized hypertensive patients it increased significantly with 10 mg and 30 mg of nifedipine from 66 3 to 80 3 beats/minute ($p < 0\ 001$) (n = 7) and 70 0 to 82 2 beats/minute ($p < 0\ 01$) (n = 9) respectively (Table III Fig 3) Combined administration of nifedipine and propranolol decreased the heart rate from 67 5 to 65 5 beats/minute (n = 8) one hour after administration Therefore propranolol seems to inhibit a nifedipine induced increase in heart rate associated with a decrease in blood pressure

Effect of nifedipine on blood pressure and heart rate After administration of either nifedipine alone or with propranolol normotensive patients showed slight changes in both systolic and diastolic pressure within 5 minutes Decrease continued reaching the lowest levels after 60 minutes (Fig 1)

Fall of both systolic and diastolic pressure starts within 5 minutes in hypertensive patients decreases for one to two hours reaching relatively rapidly almost normotensive levels Then blood pressure increases gradually and reaches near pretreatment values within six to ten hours (Fig 2)

In normotensive patients heart rate increases rapidly to reach the highest rate within 30 minutes and returns to the initial rate after two hours In contrast the heart rate increases rapidly to reach the highest within 30 minutes and gradually decreases however it remains slightly elevated for ten hours in hypertensive patients (Fig 3)

Hypotensive effect and heart rate increase In 24 hypertensive patients (total of hospitalized and outpatients) nifedipine (30 mg) lowered both the systolic and diastolic blood pressures significantly and increased the heart rate as shown in Table IV The differences in both blood pressure and heart rate are statistically significant

Plasma renin activity increase by nifedipine and its inhibition by propranolol Plasma renin activity in normotensive subjects increased from 1 3 to 2 0 ng /mg /hour ($p < 0\ 02$) 276 per cent after 10 mg nifedipine and from 1 4 to 4 1 ng /mg /hour ($p > 0\ 1$) 237 per cent after 30 mg of nifedipine On the contrary it decreased from 2 2 to 1 7 ng /ml /hour ($p > 0\ 1$) after the combined administration of nifedipine and pro

Table II Hospitalized hypertensive patients

Case No	Initial	Age (years)	Sex	Clinical diagnosis	Urinalysis protein	Urinalysis sugar	Blood urea nitrogen (mg /dl)	ECG findings $SV_1 + RV_5$ (mV)	ECG findings ST depression (mV)	ECG findings T	CTR (%)	Ocular fundus Scheie
1	R R	63	M	Ht essential	(–)	(–)	14	2 5	< 0 1	Flat	52	H S
2	I K	56	M	Ht essential	(–)	(–)	14	5 2	> 0 1	Flat	50	H, S
3	M I	38	M	Ht essential	(–)	(–)	17	5 3	Normal	Normal	51	H, S
4	T O	43	M	Ht essential	(–)	(–)	27	9 4	LV strain pattern		6,	H S
5	T I	47	M	Ht essential	(–)	(–)	12	4 5	< 0 1	Normal	44	H S
6	H N	54	M	Ht essential	(–)	(–)	12	7 2	Normal	Flat	68	
7	K N	36	F	Ht essential	(–)	(–)	14	2 1	Normal	Normal	50	H S
8	T K	35	M	Ht ch nephritis	(+)	(–)	26	5 0	> 0 1	Flat	50	H S,
9	Y N	29	M	Ht renal arterial stenosis	(–)	(–)	7	4 0	Normal	Normal	49	H S
10	S K.	48	M	Ht diabetes mellitus	(–)	(+ +)	24	3 5	<0 1	Inverted	50	H S
Mean ± SD		44 9 ± 10 7					16 7 ± 6 7	4 9 ± 2 2			53 1 ± 7 9	

Abbreviations Ht = hypertension M = male F = female ch = chronic

x ray 53 1 ± 7 9 per cent (44 to 68 per cent) ocular fundus in Scheie H_1 to H_4 (Table II)

All medications were discontinued at least two weeks prior to admission to the study In four normotensive volunteers (Table I) and in ten hospitalized hypertensive patients (Table II) blood pressure heart rate and plasma renin activity were determined as follows (1) they received sublingually 10 mg of nifedipine (Adalat, Bayer), (2) after one week of administration the dose was increased to 30 mg nifedipine sublingually (3) after one more week a combination of nifedipine and propranolol 30 mg and 0 2 mg / Kg body weight was administered The drugs were given after at least 30 minutes bed rest when the steady state had been established Blood pressure and heart rate were measured before and after administration at 10 minute intervals during the first hour and 30 or 60 minute intervals for the subsequent 10 hours However, for normotensive subjects checks were stopped four hours after administration of the drugs Plasma renin activity before and up to 4 hours were determined

Fourteen patients were seen at our outpatient clinic They had bed rest for one hour to establish the steady state Then, nifedipine was given sublingually in a dose of 30 mg Blood pressure, heart rate and plasma renin activity were checked up to four hours after administration One week later they again visited our cardiovascular laboratory and were allowed to rest in the supine position for one hour Blood samples were taken for plasma renin activity Five minutes later 40 mg of furosemide were given intravenously The patients remained in the upright position for one hour and then blood again was collected

Plasma renin activity was determined by a slight modification of the method of Haber and associates[15] using Dainabot Kit Renin activity was expressed in ng of angiotensin I generated per ml of plasma per hour

For statistical analysis, t tests for paired data were applied and percentage averaged changes were calculated for each paired data

Results

Antihypertensive effect of nifedipine and combined administration of nifedipine and propranolol *Following administration of 10 mg* of nifedipine blood pressure in normotensives (n = 4) changed from 119 0 ± 5 3 to 120 0 ± 6 5 systolic and from 78 0 ± 4 0 to 74 5 ± 6 0 mm Hg diastolic for one hour after administration The administration of both 10 mg and 30 mg of nifedipine did not produce statistically significant changes in blood pressure in the normotensive group However blood pressure fell significantly (12 per cent in systolic p < 0 01 9 per cent diastolic p < 0 05) following combined administration of 30 mg of nifedipine and 0 2 mg /kg body weight of propranolol (Table I and Fig 1)

In hospitalized hypertensive patients blood

Table III Effects of Ca² antagonist (nifedipine) and beta blockade (propranolol) on blood pressure heart rate and PRA* in hospitalized hypertensive patients

Treatment		Nifedipine 10 mg						Nifedipine 30 mg						Nifedipine 30 mg and Propranolol 0.2 mg/kg body wt					
		Blood pressure (mm Hg)		Heart rate (beats/min)		PRA (ng/ml/h)		Blood pressure (mm Hg)		Heart rate (beats/min)		PRA (ng/ml/h)		Blood pressure (mm Hg)		Heart rate (beats/min)		PRA (ng/mL/h)	
Case No†		B	1 hour	B	1 hour	B	1 hour	B	1 hour	B	1 hour	B	1 hour	B	1 hour	B	1 hour	B	1 hour
1	S	1"0	150	72	90			150	110	6	,4	0 3	4 0						
	D	130	110					130	94										
2.	S	168	1?0	7?	80			170	140	66	80	0 5	1 0	154	1?0	66	60	0 7	0 1
	D	100	80					100	80					96	74				
3.	S	200	130	6?	96			186	130	,0	100			196	110	64	"0		
	D	120	80					1?0	90					120	80				
4	S	150	110	52	54			150	100	6r	0			150	94	52	56	0 8	0 6
	D	100	0					110	60					90	68				
5	S	190	1?2	66	90			190	140	,0	84	(1? 4)		190	122	76	70	17.9	11 5
	D	130	104					130	90					130	80				
6.	S	172	130	78	80			156	128	"0	80	? 3	3 2	170	136	76	7?	4 0	1 7
	D	110	8?					108	84					110	90				
7	S	160	120	6?	72			160	110	64	6	2 9	4 2	160	110	64	64	2 4	1.5
	D	100	80					100	,0					100	70				
8.	S							190	120	7?	86	0 2	0.3						
	D							120	80										
9	S							150	1?0	,6	90			150	112	8?	78	4 5	2 4
	D							100	80					90	70				
10	S													200	1?4	60	54	1.3	0 7
	D													130	60				
	SM	172.9	130 3	66 ?	80 3			166 9	1?? 0	0 0	82 2	1 2	2 5	171 3	116 0	67 5	65 5	4 5	2 6
	± SD	17 1	15 7	8 6	14 1			17 6	13 8	4 ?	9 1	1 3	1 8	21 1	12.5	9 ?	8 4	6 1	4 0
	p value	< 0 001 s		< 0 001 s				< 0 001 s		< 0 01 s			ns	< 0 001 s		ns		ns	
	DM	112 9	86 6					113 1	80 9					108 3	,4 0				
	± SD	13 8	14 6					1 3	10 6					16 8	9 2				
	p value	< 0 01 s						< 0 001 s						< 0 01 s					
Average of paired % change of control value																			
	SM		75		121				73		117		393		68		98		5?
	± SD		7		19						12		5 6		9		8		20
	DM		77						2						70				
	± SD		6						9						12				
No of cases			(7)		(7)				(9)		(9)		(5)		(8)		(8)		(7)

Abbreviations PRA = plasma ren n t vity M = m an SD = stand rd d viat of the me n s = statist ally significant ns = not statistically significant S = systolic blood pressure D = diastol blood pressure SM = mean of sy tolic blood pressure DM = me n f diastolic blood pressure

†Age of patients (M ± SD) = 44 9 t 10 y ars (nge from 29 t 63 years) (n = 10)

tively Systolic blood pressure did not change and diastolic pressure slightly increased by propranolol administration alone [8] Heart rate decreased from 69 ± 3 beats/minute to 57 ± 1 in normotensive volunteers and was 64 ± 1 beats/minute to 56 ± 2 in hypertensive subjects respectively

The time course of plasma renin activity changes with nifedipine reaching the maximum value between one and two hours after administration and returns to initial levels within three

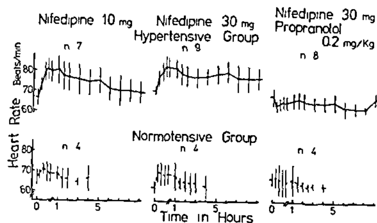


Fig 3 Heart rate increase with nifedipine in normotensive volunteers and hypertensive patients Combined administration of nifedipine and propranolol does not result in an increase in heart rate Propranolol may inhibit the increase of *the nifedipine induced increase in heart rate* Hypertensive patients = (——) normotensive volunteers = ( ) Values are mean ± standard deviation

pranolol (Table I) In hypertensive patients plasma renin activity increased from 1 2 to 2 5 (n = 5) (p > 0 1) 393 per cent after 30 mg of nifedipine and *decreased from 4 5 to 2 6 ng/ml/hour* (n = 7) (p < 0 1) 52 per cent after the combined administration (Table III) These results indicate that a nifedipine induced increase of plasma renin activity is completely inhibited by propranolol

The time course of plasma renin activity changes is shown in Table IV Nifedipine causes increase of plasma renin activity for two hours followed by a gradual decrease, corresponding with a persisting decrease in blood pressure (Table IV) As the result of furosemide and the upright posture the plasma renin activity is significantly increased (Table IV)

Discussion

Our previous studies have shown that nifedipine is a potent antihypertensive agent [12] Klutsch and colleagues [16] Kobayashi and associates [17] and Murakami and co workers[18] have also reported on the hypotensive effect of nifedipine In this study this is again confirmed Higher doses (30 mg) are more effective than lower doses (10 mg)

Ca antagonists (nifedipine, verapamil and others) have been investigated for their hypotensive effect [1 14 16 18] The pharmacological action of verapamil is thought to block primarily the slow inward calcium current in ventricular fibers [19] and Ca influx associated with excitation [2] Similary, the negative inotropic action of nifedipine seems to block the slow calcium inward current [9 10] Hemodynamic effects of nifedipine are summaried by the following (1) marked reduction in arterial pressure,[12 14 16 18] (2) increase in heart rate,[1] (3) decrease in peripheral vascular resistance,[18 1] (4) increase in coronary blood flow,[21] and (5) increase in cardiac output and stroke volume [16 2] (6) Diuresis, urea clearance and electrolyte clearance, are increased by nifedipine in hypertensive patients due to an increase in the glomerular filtration rate and renal plasma flow [16] Nifedipine has a controlled negative inotropic action by antagonizing the excitation-contraction coupling Thus cardiac function and peripheral vascular resistance are reduced

Hypertension is generally associated with increased cardiac function and elevated peripheral vascular resistance therefore it seems logical to reduce both cardiac activity and vascular tone, when managing hypertensive patients Considering these points, Ca[2] antagonists can be assumed to be logical drugs for the treatment of essential hypertension, especially the severe *forms*

Besides lowering blood pressure nifedipine increases the heart rate This transient increase can be apparently inhibited by propranolol It has been shown that vasodilators such as nifedipine [1] verapamil [13 14] diazoxide [1] PDP [4] and hydralazine [5] increase the heart rate probably by enhancing sympathetic discharge via the vasoreceptors [4 8] The most common side effect of nifedipine was the effect on the vessels and heart which were headache (4 5 per cent) facial flushing (3 1 per cent) giddiness (1 7 per cent) and palpitation (5 per cent) These side effects were almost abolished or inhibited by the combination administration of nifedipine and propranolol The combined administration of nifedipine and propranolol for the treatment of hypertension may therefore be *recommended Propranolol alone* was given intravenously (0 2 mg/Kg body weight) in 11 normotensive healthy men and in 13 patients with essential hypertension (mild) and their blood pressure and heart rate was measured before propranolol and 5 15 30 and 60 minutes after propranolol Blood pressure (mean ± SEM) was 120 ± 3/66 ± 3 mm Hg and 114 ± 3/71 ± 2 112 ± 3/72 ± 3 114 ± 4/72 ± 3 114 ± 3/71 ± 2 mm Hg in normotensive healthy volunteers and was 145 ± 4/93 ± 3 mm Hg and 146 ± 4/99 ± 4 142 ± 4/97 ± 3, 143 ± 4/98 ± 3 and 148 ± 4/ 98 ± 3 mm Hg in hypertensive subjects respec

in both normotensive and hypertensive patients

The antihypertensive effect of nifedipine is enhanced and prolonged by propranolol The observed increase in heart rate and plasma renin activity with nifedipine is inhibited by propranolol probably by inhibiting the cardiovascular effects of the activity of the sympathetic nervous system

The results of this study indicate that oral administration of nifedipine is very effective in lowering arterial blood pressure in hypertensive patients especially when combined with propranolol

Administration of nifedipine with beta blockade resulted in satisfactory management of hypertension with minimal adverse drug reactions which could be possibly attributed to the preparation especially in the management of hypertensive emergencies including hypertension associated with acute myocardial infarction and coronary insufficiency

We wish to thank Dr H J Knoblich and Prof K Hotta for assistance in preparation of the manuscript

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Table IV Decrease of blood pressure, increase of heart rate and PRA* by Ca^{2+} antagonist (30 mg of nifedipine) and increase of PRA by 40 mg of furosemide in the upright position in hypertensive group

		Nifedipine 30 mg						*Furosemide 40 mg upright position*	
		Before	*30 min*	*1 hour*	*2 hours*	*3 hours*	*4 hours*	*Before*	*1 2 hours*
Systolic Blood pressure mm Hg	M	176.3	145.2	125.2	124.0	119.6	120.8		
	SD	23.8	16.6	15.5	16.1	15.8	5.8		
	p value		< 0.02 s	< 0.001 s	< 0.001 s	< 0.01 s	< 0.001 s		
Diastolic	M	109.5	88.4	79.6	79.9	72.8	76.8		
	SD	15.1	7.4	11.2	12.7	10.0	10.1		
	p value		< 0.05 s	< 0.001 s	< 0.001 s	< 0.01 s	< 0.01 s		
Heart rate beats/min	M	73.3	85.2	84.1	82.2	72.2	77.4		
	SD	10.1	15.0	10.0	10.9	10.0	10.2		
	p value		< 0.05 s	< 0.001 s	< 0.001 s	> 0.1 ns	> 0.1 ns		
Plasma renin activity ng/ml/h	M	1.75	2.87	2.95	2.99	1.60	1.37	2.32	3.43
	SD	2.45	4.13	4.01	4.90	1.55	2.26	5.38	5.60
	p value		> 0.1 ns	< 0.01 s	< 0.05 s	> 0.1 ns	< 0.05 s		< 0.01 s
No of patients		(24)	(5)	(21)	(20)	(5)	(8)	(17)	

See Tables I to III for explanation of abbreviations

hours, while decreased pressure persisted (Table IV Fig 2) Propranolol inhibits this increase of plasma renin activity but does not inhibit the decrease of blood pressure Negative correlations between changes of plasma renin activity and blood pressure levels following administration of nifedipine, are noted However there is a positive correlation when nifedipine and propranolol are combined These results suggest that plasma renin activity changes may be caused mainly by renin release from the kidney due to increase of sympathetic discharge by vasodilators ' However renin release is controlled by a number of factors including vascular receptors muscular tone, sympathetic nervous system, perfusion pressure to the renal arterioles and its wall tension so a conclusion with regard to the effect of nifedipine on plasma renin activity may not be drawn

Summary

The effect of the administration of a cardiovascular Ca antagonist (nifedipine) on arterial blood pressure, heart rate and plasma renin activity was investigated

Blood pressure of normotensive healthy volunteers (n = 4) does not change significantly by administration of 10 mg (from 119/78 to 120/75 mm Hg) and 30 mg (from 114/69 to 105/66 mm Hg) of nifedipine When nifedipine (30 mg) is administered with propranolol (beta blockade), a slight decrease of systolic and diastolic blood pressure was observed (from 119/73 to 104/61 mm Hg) Blood pressure of hypertensive patients is significantly lowered by 10 mg of nifedipine from 172.9 to 130.3 mm Hg (25 per cent reduction) systolic and from 112.9 to 86.6 mm Hg (23 per cent) diastolic (n = 7) Thirty mg nifedipine had a slightly stronger hypotensive effect namely 27 per cent reduction in systolic and 28 per cent in diastolic values (n = 9) Combined administration of nifedipine and propranolol resulted in lowering initial blood pressure by 32 per cent and 30 per cent reduction in systolic and diastolic (n = 8) respectively

The heart rate of normotensive patients hardly changes with administration of 10 and 30 mg of nifedipine and combined medication But in hypertensive subjects it is significantly increased by nifedipine from 66.3 to 80.3 ($p < 0.001$) by 10 mg and from 70.0 to 82.2 beats/minute ($p < 0.01$) by 30 mg On the contrary combined administration of nifedipine and propranolol causes no increase or only a slight decrease in heart rate (from 68 to 66 beats/minute)

Plasma renin activity of normotensive and hypertensive subjects is increased by 30 mg of nifedipine Combined administration of nifedipine and propranolol decreases plasma renin activity

Circulating catecholamines and systolic time intervals in normotensive and hypertensive patients with and without left ventricular hypertrophy

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An increase in heart rate and myocardial contractility is present in a large subgroup of patients with borderline and established hypertension and it has been suggested that the underlying mechanism for these augmented cardiac functions is an exaggerated adrenergic drive to the heart. The recent development of sensitive radioenzymatic assays for the precise measurement of catecholamines (CA) has led to the discovery that circulating CA levels are increased in a large proportion of patients with essential hypertension. It has been proposed that the population with essential hypertension is composed of two distinct sub groups: hyperadrenergic patients (those with CA above normal levels) and normoadrenergic patients (those with CA levels within normal range). Heart rate in the hyperadrenergic group was found to be higher than in the normoadrenergic group, whereas the mean heart rate from the latter group was identical to that of normotensive subjects. There is a possibility that these two groups of hypertensive patients with normal and high levels of circulating CA might represent separate clinical entities.

In the present study, the ventricular performance of normotensive and hypertensive patients (with or without left ventricular hypertrophy [LVH]) was evaluated with systolic time measurements and related to their basal circulating CA levels.

Methods

Fourteen normotensive patients (eleven males and three females) aged 22 to 50 years (mean 36.8 ± 2.7 years) and 43 hypertensive patients (25 males and 18 females) aged 23 to 52 years (mean 39.3 ± 2.0 years) were studied between 1:00 and 2:00 P.M. Patients had received no medication for at least 2 months prior to the study.

Patients were diagnosed as having essential hypertension after exclusion of known causes of hypertension. Hypertensive patients were subdivided into two groups according to the presence or absence of left ventricular hypertrophy (LVH) determined by electrocardiogram, chest x rays, and echocardiography. Seven hypertensive patients had evidence of LVH but no signs of left ventricular failure, while 36 patients had no LVH. Mean age values did not differ significantly between patients without LVH (38.9 ± 1.9 years) and those with LVH (41.2 ± 3.2 years).

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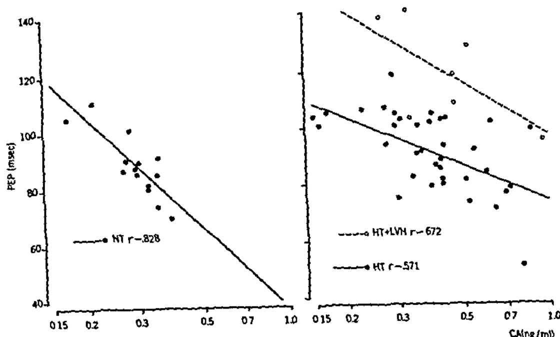


Fig 2 Correlation between the logarithm of plasma catecholamines and preejection period Patients are those illustrated in *Fig 1* For the HT + LVH group intercept differs significantly when compared with NT or HT groups (P < 01)

terval index LVETI did not differ significantly between normotensive and hypertensive patients without LVH but mean PEP and PEP/LVET values were significantly higher and LVET value significantly lower in hypertensive patients with LVH

Correlation coefficients between logarithm of plasma CA and systolic time intervals heart rate and blood pressure for the three groups of patients are given in Table II Within each group there were good correlations between plasma CA and PEP or PEP/LVET values In hypertensive patients with LVH the intercept of the regression line between plasma CA and PEP was significantly higher than in hypertensive patients without LVH indicating a relationship between circulating CA and higher PEP values (Fig 2) Correlations were poor between plasma CA and LVET systolic or diastolic blood pressure in the three groups of patients For the group of hypertensive patients without LVH there was a good correlation between plasma CA and heart rate (Fig 3)

When hypertensive patients were subdivided into normoadrenergic (circulating CA levels within the normotensive range) and hyperadrenergic (circulating CA levels above normal range) groups significant differences were observed in some cardiac functions Mean heart rate was significantly higher in the hyperadrenergic group than in normotensive subjects but was not different in the group of normoadrenergic patients Mean PEP and PEP/LVET values were significantly higher for the normoadrenergic group when compared with normotensive pa

Table II Correlation coefficients between logarithm of circulating CA and systolic time intervals, heart rate and blood pressure in normotensive (NT) and hypertensive patients without LVH (HT) or with LVH (HT + LVH)

	PEP	*LVET*	*PEP/LVET*	*Heart rate*	*Systolic blood pressure*	*Diastolic blood pressure*
NT (n=14)	−828	−0[illegible]2	−.58[illegible]	097	3[illegible]1	365
HT (n=36)	−571	−487	−415	538	−278	−.30[illegible]
HT + LVH (n=7)	−672	−193	−584	−405	−006	.332

Table I Mean values of circulating CA, systolic time intervals systolic time interval index, heart rate, and blood pressure in normotensive (NT) and hypertensive patients without LVH (NT) or with LVH (HT + LVH)

	CA (ng /ml)	PEP (msec)	LVET (msec)	LVETI (msec)	PEP/ LVET	Heart rate (beats/ min)	Systolic blood pressure (mm Hg)	Diastolic blood pressure (mm Hg)
NT (n = 14)	305 ± 0 15†	88 2 ± 3 0	292 4 ± 5 8	412 2 ± 3 9	306 ± 010	70 9 ± 2 4	119 3 ± 3 4	61 ± 25
HT (n = 36)	434 ± 030*	90 2 ± 2 3	278 5 ± 4 5	418 3 ± 2 6	325 ± 005	85 1 ± 2 7**	155 5 ± 3 8**	99 1 ± 25
HT + LVH (n = 7)	524 ± 104	117 1 ± 6 8*	272 3 ± 9 0*	414 7 ± 7 3	442 ± 032*	83 6 ± 5 1**	180 0 ± 12 5	105 7 ± 3

†Mean ± SEM
P < 05
P < 01 versus values in normotensive subjects

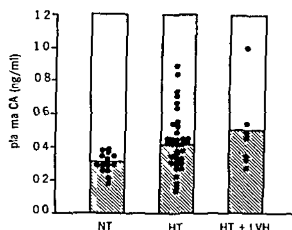


Fig 1 Circulating catecholamines at rest in normotensive subjects (*NT* n = 14) hypertensive patients without left ventricular hypertrophy (*HT* n = 36) and *hypertensive* patients with left ventricular hypertrophy (*HT + LVH* n = 7) *The shaded area* at the bottom of each rectangle represents the average levels for all values of each group

carotidogram pulse tracing were recorded simultaneously after resting supine for 20 minutes All tracings were made at a paper of 100 mm /sec on a three channel Schwarzer recorder Ten consecutive cardiac cycles were analyzed to determine the average heart rate Q S interval and left ventricular ejection time The Q S_2 interval was measured from the beginning of the Q wave to the first rapid deflection of the second heart sound The left ventricular ejection time (LVET) was measured from the onset of the rapid stroke of the carotid pulse to the nadir of the dicrotic notch The preejection period (PEP) was calculated by substracting LVET from the Q S interval The corresponding systolic time interval index (LVETI) was calculated from LVET value according to the formula LVETI LVET + 1 6 × heart rate (females), LVETI LVET + 1 7 × heart rate (males)[10] PEP and PEP/LVET do not depend to a significant extent upon the heart rate and no correction was made[11 14] Blood pressure was determined by indirect sphygmomanometry At the end of the resting period, 7 milliliters of blood were sampled from a brachial vein in a non heparinized tube for the determination of circulating catecholamines

The same tests were repeated two weeks later for 10 of the patients (five normotensive and five hypertensive subjects)

Circulating CA levels were measured by the radioenzymatic method of Coyle and Henry[15] modified for measurements in plasma[8] The principle of this technique is based on the conversion of the norepinephrine and epinephrine to tritiated normetanephrine and metanephrine in the presence of catechol O methyl transferase and tritiated S adenosylmethionine as a labelled methyl donor The technical details for this method have been previously described[8]

For statistical evaluation the Student s t test the Pearson r test and covariance analysis were used

Results

Mean values for circulating CA systolic time intervals systolic time interval index, heart rate and blood pressure for normotensive patients and the two groups of hypertensive patients are given in Table I The mean circulating CA level was significantly higher for the two groups of hypertensive patients with or without LVH (Fig 1) Mean values for systolic time intervals (PEP LVET PEP/LVET) and the systolic time in

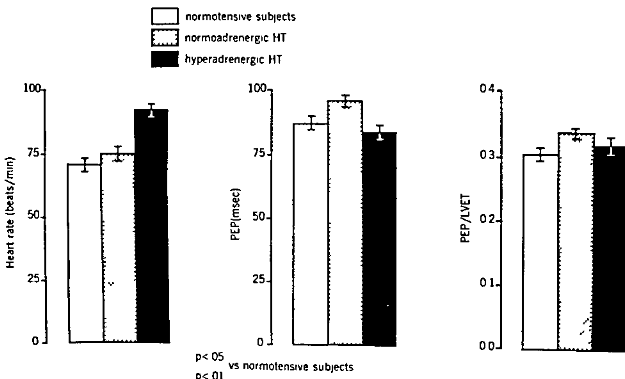


Fig 4 Heart rate preejection period and PEP/LVET (Mean±SEM) in hypertensive patients without left ventricular hypertrophy subdivided in two groups a normoadrenergic group (circulating CA within the normotensive range 17 patients) and a hyperadrenergic group (circulating CA levels above normal levels 19 patients)

Table III Mean values of circulating CA systolic time intervals systolic time interval index heart rate and blood pressure in normoadrenergic hypertensive patients (circulating CA levels within the normotensive range) and hyperadrenergic hypertensive patients (circulating CA levels above the normotensive range)

	CA (ng/ml)	PEP (msec)	LVET (msec)	LVETI (msec)	PEP/LVET	Heart rate (beats/min)	Systolic blood pressure (mm Hg)	Diastolic blood pressure (mm Hg)
Normoadrenergic group (n = 1)	?96 ± 018	96 8 ± 2 7	29? 3 ± 5 4	417 8 ± 4 1	.331 ± 004	?6 3 ± 3 0	15 6 ± 5 2	100 ? ± 3 3
Hyperadrenergic group+ (n = 19)	5?8 ± 03?	84 4 ± 3	264 ? ± 4 3	417 5 ± 3 3	319 ± 006	93 0 ± 1.9	153 7 ± 4 3	97 7 ± 2 9

P < 05
P < 01
†Ag 38 4 _ 5 ars.
‡Age 41.9 - 1 rs.

have previously reported that 40 to 50 per cent of hypertensive patients had circulating CA levels above the highest value found in normotensive subjects and we have proposed the classification of hypertensive patients into hyperadrenergic or normoadrenergic groups based on whether resting circulating CA levels were above or within the normal range In the present study and as previously reported hyperadrenergic hyperten sive patients were found to have higher heart rates than normotensive or normoadrenergic hypertensive patients Moreover circulating CA levels were closely correlated with heart rate in hypertensive patients The normoadrenergic group of hypertensive patients was also found to have significantly higher PEP and PEP/LVET

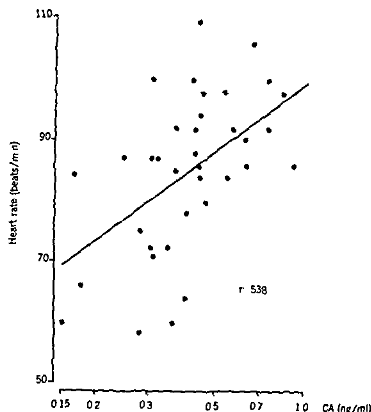


Fig 3 Correlation between the logarithm of plasma catecholamines and heart rate in hypertensive patients without left ventricular hypertrophy (*HT* n = 36)

tients, but were not significantly different in the hyperadrenergic group (Fig 4)

When normoadrenergic and hyperadrenergic groups were compared heart rate was found to be significantly higher in the latter group, while PEP and PEP/LVET were significantly lower LVET was also significantly lower in the hyperadrenergic group but LVETI was not different Mean diastolic and systolic blood pressure values were similar for both groups (Table III)

Circulating CA systolic time intervals heart rate and blood pressure tests were repeated two weeks later under identical conditions in five normotensive and five hypertensive patients Mean circulating CA levels of both groups were identical in the first and second study and circulating CA levels remained significantly higher in hypertensive patients (Fig 5) Systolic time intervals heart rate and blood pressure were also similar in both series (Table IV)

Discussion

Systolic time intervals such as PEP and PEP/LVET, have proved to be good index of myocardial contractility in the healthy human and in patients with hypertensive disease[11, 16, 17] The sympathetic system is probably the most important factor regulating the position of the force-velocity and ventricular performance curves under physiological conditions[1] The measurement of circulating CA is highly stable and reproducible when determined under standardized conditions[8] Circulating CA systolic time intervals blood pressure, and heart rate were similar in the same patients tested at the beginning of the study and after a two week interval Moreover, circulating CA levels were found to increase in conditions known to activate the sympathetic system such as tilting[19] and dynamic exercise[20] thus supporting the validity of circulating CA as an index of sympathetic activity In the present study, circulating CA levels were inversely related with PEP or PEP/LVET therefore suggesting a good correlation between myocardial contractility and circulating CA This finding is in agreement with our previous studies in which coronary sinus CA were correlated with myocardial contractility directly determined with the dP/dt of left ventricular pressure[21] The validity of this correlation is also supported by the observation that infusion of CA in the human shortens PEP and PEP/LVET[11 23] Since part of the neurally released CA diffuses into the circulation circulating CA may give a relative indication of the amount of physiologically active CA present at the receptor Good correlations between circulating CA and myocardial contractility further support that the measurement of circulating CA provides a good index of sympathetic activity in the human under standardized conditions

In hypertensive patients with LVH the mean PEP value was significantly higher than in hypertensive patients without LVH The prolongation of PEP in hypertensive cardiopathy is secondary to a diminished rate of isovolumic left ventricular pressure rise[1] This could explain the inverse relationship between circulating CA levels and higher PEP values in hypertensive patients with LVH during a period of altered myocardial contractility

When the group of hypertensive patients without LVH was taken as a whole there was no significant difference for the mean PEP or PEP/LVET value when compared with normotensive subjects, in agreement with previous studies However, when these hypertensive patients were further subdivided according to their circulating CA levels significant differences appeared We

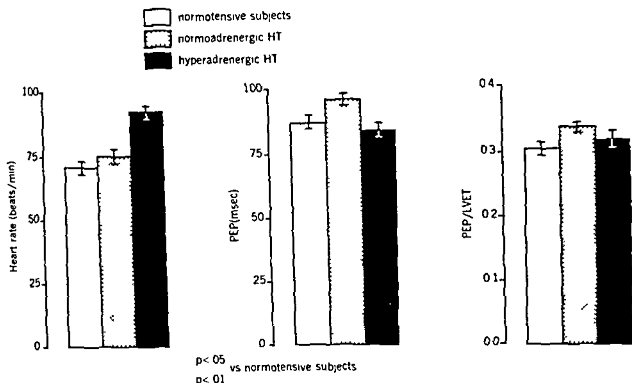


Fig 4 Heart rate preejection period and PEP/LVET (Mean ± SEM) in hypertensive patients without left ventricular hypertrophy subdivided in two groups a normoadrenergic group (circulating CA within the normotensive range 17 patients) and a hyperadrenergic group (circulating CA levels above normal levels 19 patients)

Table III Mean values of circulating CA systolic time intervals systolic time interval index heart rate and blood pressure in normoadrenergic hypertensive patients (circulating CA levels within the normotensive range) and hyperadrenergic hypertensive patients (circulating CA levels above the normotensive range)

	CA (ng/ml)	PEP (msec)	LVET (msec)	LVETI (msec)	PEP/LVET	Heart rate (beats/min)	Systolic blood pressure (mm Hg)	Diastolic blood pressure (mm Hg)
Normoadrenergic group† (n = 17)	296 ± 018	96 8 ± 2	29? 3 ± 5 4	417 8 ± 4 1	331 ± 004	76 3 ± 3 0	15? 6 ± 5 2	100 7 ± 3.3
Hyperadrenergic group‡ (n = 19)	558 ± 035	84 4 ± 3 [illegible]	264 7 ± 4 3	417 5 ± 3 3	319 ± 006	93 0 ± 1 9	153 7 ± 4.3	9? 7 ± ?9

P < 05
P < 01
†Age 38 4 ± 2 5 years
‡Age 41.9 ± [illegible] years.

have previously reported that 40 to 50 per cent of hypertensive patients had circulating CA levels above the highest value found in normotensive subjects and we have proposed the classification of hypertensive patients into hyperadrenergic or normoadrenergic groups based on whether resting circulating CA levels were above or within the normal range In the present study and as previously reported hyperadrenergic hypertensive patients were found to have higher heart rates than normotensive or normoadrenergic hypertensive patients Moreover circulating CA levels were closely correlated with heart rate in hypertensive patients The normoadrenergic group of hypertensive patients was also found to have significantly higher PEP and PEP/LVET

Table IV Mean values of circulating CA, systolic time intervals, heart rate, and blood pressure in five normotensive and five hypertensive patients repeated at an interval of two weeks under identical conditions

	CA (ng/ml)	PEP (msec)	LVET (msec)	Heart rate (beats/min)	Systolic blood pressure (mm Hg)	Diastolic blood pressure (mm Hg)
Normotensive						
1st study	274 ± 02	973 ± 60	2940 ± 84	667 ± 10	1125 ± 32	712 ± 31
2nd study	268 ± 03	922 ± 58	2957 ± 104	682 ± 41	1112 ± 31	712 ± 43
Hypertensive						
1st study	436 ± 04	1064 ± 154	2690 ± 143	840 ± 65	1510 ± 90	960 ± 68
2nd study	435 ± 05	1034 ± 109	2788 ± 136	832 ± 78	1520 ± 124	930 ± 70

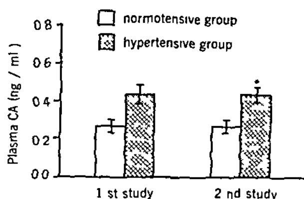


Fig 5 Circulating catecholamines in five normotensive and five hypertensive patients measured at an interval of two weeks Bars represent mean ± SEM $P < 0\,05$

values than the group of normotensive patients while these values were not significantly different in the hyperadrenergic group

When normoadrenergic and hyperadrenergic groups were compared, PEP and PEP/LVET were significantly lower in the hyperadrenergic group Since mean diastolic blood pressure was similar in both groups it is then likely that lower PEP and PEP/LVET values in the hyper adrenergic group reflect an enhanced myocardial contractility in these patients

These findings are in good agreement with a previous study where approximately 40 per cent of hypertensive patients were found to have higher heart rates than normotensive patients and similar values for PEP and PEP/LVET [2] According to these authors 'normal PEP and PEP/LVET in this group of patients designated hyperkinetic essential hypertension,' would indicate in the presence of an elevated diastolic blood pressure an increased rate of rise in ventric ular pressure and they suggested that these augmented cardiac functions were secondary to an exagerated adrenergic drive to the heart High levels of circulating CA observed in our study for this group of patients further substantiated this hypothesis

The hyperadrenergic group of hypertensive patients probably correspond to high renin hypertensive patients, since high circulating CA levels were recently observed in a group with mild high renin essential hypertension [3] This group of high renin hypertensive subjects also had lower PEP and higher heart rate values

The increased chronotropic and inotropic myocardial activity induced by sympathetic stim ulation is associated with an increased myocar dial oxygen consumption [25,26] High levels of circu lating CA in hyperadrenergic hypertensive patients could have a deleterious effect on a myocardium already subjected to an increased afterload A greater incidence of sudden deaths and cardiac diseases have been reported in indi viduals with rapid heart rate [21] It is therefore possible that higher circulating CA levels might contribute to a higher incidence of cardiovascular disease in the group of hyperadrenergic hyperten sive patients

Circulating CA levels then appear to be a good index of sympathetic activity in man as suggested by good correlations with myocardial contractility index such as PEP and PEP/LVET Moreover basal circulating CA levels are highly reproducible when repeated under standardized conditions A large subgroup of patients with essential hypertension are characterized by increased chronotropic and inotropic myocardial functions and elevated circulating CA levels thus suggesting that they constitute a separate clinical entity

Summary

Circulating catecholamine (CA) levels were measured in normotensive and hypertensive patients with or without left ventricular hypertrophy (LVH) and were related with systolic time intervals heart rate and blood pressure The pre ejection period (PEP) and the ratio PEP/LVET were correlated with circulating CA in normotensive and hypertensive patients For a given circulating CA level the PEP was higher in hypertensive patients with LVH than in those without LVH This is probably secondary to a diminished myocardial contractility in these patients Heart rate was related with circulating CA in hypertensive patients without LVH When hypertensive patients without LVH were divided into normoadrenergic (circulating CA levels within normotensive range) and hyperadrenergic (circulating CA above normal range) groups the hyperadrenergic group was found to have significantly higher heart rate than normotensive patients while the heart rate of the normoadrenergic group was similar to that of the normotensive group PEP and PEP/LVET were significantly elevated in the normoadrenergic group when compared with normotensive subjects but were not different in the hyperadrenergic group These differences in chronotropic and inotropic myocardial activity between these two groups of hypertensive patients with normal and high levels of circulating CA suggest that they are separate entities

The authors are most grateful to Ms Diane Papin and Jo Anne Le Guerner for their skillful technical assistance and to Ms. Marie Colette Renaud and June Manson for their efficiency in preparing the manuscript

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Case reports

Electrophysiologic-histologic correlation of the cardiac specialized conduction system in two cases of single ventricle and levotransposition of the great arteries

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John Fenoglio M D
Ehud Krongrad M D F A C C
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Electrophysiologic delineation of the specialized cardiac conduction system (SCS) during open heart surgery has been found to be a valuable technique for locating the cardiac conduction system in patients with various forms of congenital heart disease This technique was found useful particularly in patients in whom extensive intraventricular repair is carried out during open heart surgery In such patients the use of this technique assumes special clinical importance The technique is especially helpful in patients in whom the specialized conduction system is known to vary in location such as in patients with single ventricle and therefore enables surgical repair of this complex anomaly considered until recently inoperable Although in recent years many studies reported observations on recording specialized conduction system electrograms in man during cardiac catheterization as well as during open heart surgery we are unaware of previous reports correlating the location of specialized conduction system electrograms obtained during open heart surgery under direct vision with histologic verification of the underlying conducting tissue

The purpose of this report is to present the electrophysiological observations in two cases with single ventricle (type A)[1] obtained during open heart surgery and to verify these findings with histological examination of the specialized conduction system

From the Departm nts f Pharma l gy nd Ped atrics C ll g f Physicia & Su geon of Col mb U v rsity New Yo k N Y and the Department f Card scul P thol gy Armed F rces I st tute of P thol gy Washingt n D C

Supported in part by gr nt HF 1 38 08 fr m th Nat l H rt a d Lu g Inst tute U ited States Public He lth S rv e

Recei ed f publ tion Ju 8 1977

Accepted f publ cation July 6 1977

Reprint requests to Eh d Kro grad M D Bab es Hosp tal (BHA1 107) 3975 Broadway New Y rk N Y 10032

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Case reports

Case 1 L S was known to have levotransposition of the great arteries and a large interventricular communication documented by cardiac catheterization in early life Because of congestive heart failure and to protect the pulmonary vascular bed from developing pulmonary vascular disease pulmonary artery banding was carried out at 14 months of age At age 13 years she was referred for elective surgical closure of the intraventricular defect Throughout the patient s entire life she had maintained a normal sinus rhythm (Fig 1)

During open heart surgery the patient was placed on total cardiopulmonary bypass and a ventriculotomy was performed Inspection of the intraventricular anatomy showed both A V valves to enter a large single ventricular chamber There was also a subaortic infundibular chamber which was connected to the other ventricular chamber via a bulboventricular foramen

Intraventricular delineation of the specialized conduction system was then carried out as previously described demonstrating specialized conduction system electrograms between the bulboventricular foramen and the pulmonary valve Identification of the specialized conduction system was carried out during sinus rhythm and also during atrial pacing at 92 beats per minute with 1 1 atrioventricular conduction (Fig 2) The longest interval from specialized conduction system electrogram to the initial deflection of the QRS complex was 43 msec A Teflon patch was th n sewn in dividing the single ventricle into two chambers An outflow patch was also sewn from the

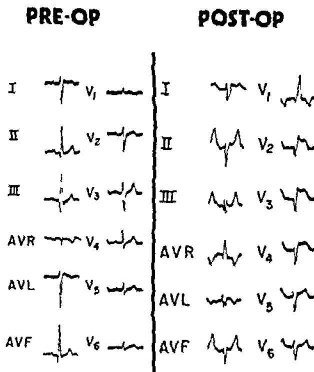


Fig 1 Pre and postoperative electrocardiogram of the patient L S Note normal sinus rhythm and normal A V conduction prior to and following operation In addition the postoperative electrocardiogram shows evidence of antero septal myocardial infarction with Q waves in Leads V_1 to V and S T segment elevation in Leads V_1 to V_5

reconstructed right ventricle to widen its outflow tract well into the area of the previous pulmonary artery band Following completion of surgery the patient was in normal sinus rhythm with 1 1 A V conduction The right ventricular systolic pressure at end of surgery was 35 mm Hg and the left ventricular systolic pressure 75 mm Hg Electrocardiogram done one day postoperatively showed a normal sinus rhythm with a P R interval of 0 18 sec frontal QRS axis of −120 degrees and a QRS duration of 0 12 sec compatible with intraventricular conduction delay Q waves were present in Leads V to V with ST elevation in Leads V to V compatible with acute myocardial infarction (Fig 1) Postoperatively the patient progressively developed a low cardiac output syndrome and died despite intensive therapeutic efforts

At autopsy the heart was enlarged (373 g) The aorta was anterior and to the left of the pulmonary artery (L transposition of the great arteries) Two A V valves opened into a single ventricle The intraventricular patch and the pulmonary artery outflow patch were intact A bulboventricular foramen led from the single ventricle to a small subaortic outflow chamber A false tendon like structure extended across the subaortic chamber (Fig 3) from the area where the specialized conduction system was identified by our mapping technique Foci of subendocardial hemorrhage were present over the anterior ventricular wall and anterior papillary muscle

The region of the heart in which the His bundle was identified during surgery was excised in toto and serially blocked The blocks were oriented in the frontal plane relative to the atrial septum embedded in paraffin and step sectioned collecting every twelfth section Sections were stained with hematoxylin and eosin and the Movat pentachrome stain In addition the atrial septum was excised in toto and serially blocked The blocks were step sectioned collecting every fiftieth section, and the sections were stained as above An atrioventricular node in the normal position in the posterior interatrial septum was identified This node was small and had no contact with the ventricular myocardium (Fig 4) In the area of the junction of the atrial septum and the right atrial appendage adjacent to the transposed pulmonary artery a second nodal structure (accessory or anterior atrioventricular node) was identified (Fig 5A) This collection of specialized atrial cells coalesced to form a bundle of fibers which coursed through the fibrous annulus to become the atrioventricular bundle

The atrioventricular bundle penetrated the fibrous annulus (Fig 5B) adjacent to the pulmonary valve ring and superior to the bulboventricular foramen between the main ventricular chamber and the subaortic outlet chamber In the ventricle the His bundle (Fig 5C) coursed downward on the right rim of the bulboventricular foramen and expanded into a broad sheet of fibers consistent with the normal morphology of the left bundle branch This left bundle branch then continued into the main ventricular chamber and expanded into a subendocardial network (Fig 6A) A smaller cylindrical bundle of specialized cells arising from the main bundle was identified (Fig 6B) A portion of this bundle arose above the bifurcation of the left bundle branch and transversed the upper aspect of the bulboventricular foramen in a cord like structure reminiscent of a false tendon across the outlet chamber (Fig 3) Here the specialized fibers formed subendocardial ramifications typical of the normal right bundle branch

Case 2 M K was a 13 year old girl who was known to have L-transposition of the great arteries and a single ventricle type A documented by cardiac catheterization and angiocardiography in early infancy Pulmonary artery banding was performed at 5 months of age At 8 years of age the patient developed spontaneous complete heart block (Fig 7) and at age 12 years she developed repeated bouts of staphylococcal endocarditis sensitive to oxacillin therapy She was referred for surgical repair because of increased and progressive fatigue and decreased exercise tolerance

During open heart surgery a ventriculotomy was performed with the patient on total cardiopulmonary bypass Following inspection of the intraventricular anatomy the specialized conduction system was electrophysiologically identified by observing and recording specialized conduction system electrograms preceding the QRS complex The locations where SCS electrograms were recorded were similar to the location of SCS electrograms described in Case 1—that is superior and anterior to the bulboventricular foramen

Although complete atrioventricular block was present in this patient SCS electrograms were consistently recorded and were related to ventricular electrograms at an H V interval of up to 103 msec (Fig 8) A Teflon patch was then sewn between the atrioventricular valves to divide the single ventricular cavity and care was taken not to interrupt the existing SCS An additional patch was used to widen the constriction of the pulmonary artery band and to enlarge the right ventricular" outflow tract Postoperative electrocardiograms showed (Fig 7) complete atrioventricular conduction delay identical to the previous tracing Postoperatively the

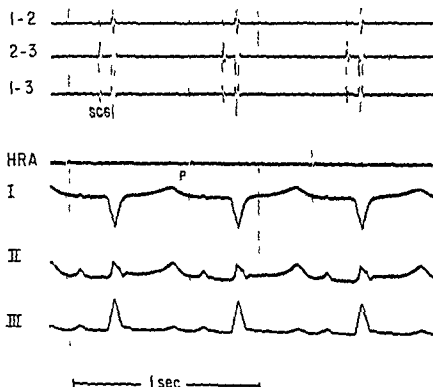


Fig 2 Specialized conduction system electrograms obtained in the patient L S during open heart surgery *The upper three tracings* show the intracardiac electrograms obtained with the electrode probe The *middle tracing (HRA)* is a high right atrial electrogram showing the pacing artifact *(P)* *The bottom three tracings are scalar* electrocardiograms Leads I II and III Note His bundle electrograms (SCS) seen between the pacing artifacts and the ventricular electrograms in each of the three cardiac cycles

patient developed progressive low cardiac output and de pite good anatomic repair and vigorous inotropic therapy she died several days postoperatively

At autopsy the heart was markedly enlarged (428 g) The aorta was anterior and to the left of the pulmonary artery Two atrioventricular valves entered the single ventricle and were separated by the Teflon patch The newly created septum and pulmonary patch were intact A bulboventricular foramen lead from the newly created left sided chamber to a small subaortic outflow chamber The conduction system was sectioned and stained in the same manner as previously described Two atrioventricular nodes were present—a hypoplastic posterior A V node in the usual po ition and an anterior node at the junction of the right atrial appendage adjacent to the pulmonary artery (Fig 9A) There was no communication of the posterior A V node with the ventricular specialized conduction system

A rudimentary atrioventricular bundle rose from the anterior node (Fig 9A) Fibers of this bundle reached the fibrous annulus but could not be traced through the fibrous ring adjacent to the pulmonary valve ring On the ventricular aspect of the fibrous ring adjacent to the pulmonary valve ring a discrete His bundle (Fig 9B) lacking any continuity with the atrioventricular bundle was identified The His bundle coursed down the right superior a pect of the bulboventricular foramen giving rise to a broad sheet of fibers which continued into the subendocardium of the main chamber and a cord like bundle of fibers (so called false tendon) that traveled from the superior anterior aspect of the bulboventricular foramen across the outlet chamber These bundles of specialized conduction tissue are the left and right bundle branches respectively and were identical to those described in Case 1

Discussion

Using the electrophysiological technique for delineation of the specialized conduction system we were able to record typical intraventricular specialized conduction system electrograms superior and anterior to the bulboventricular foramen in both cases The location of the specialized conduction system electrograms in these two patients were similar to the location of intraventricular specialized conduction system electrograms obtained by us and others in patients with corrected transposition of the great arteries two well developed ventricles and a ventricular septal defect[4,5] Further it is of interest to note that in one patient the course of the specialized conduc



Fig 3 *Gross anatomical view of the heart in first patient* RAV = right A V valve LAV = left A V valve P = pulmonary valve D = part of patch used for closure of defect The dashed area indicates the sites where specialized conduction system electrograms were obtained *The arrow* points to the false tendon extending from the bulboventricular foramen into the subaortic infundibulum Histologic examination of this structure identified it as the right bundle branch



Fig 4 Posterior atrioventricular node *(arrow)* in the normal position in the atrial septum There was no contact with the ventricular myocardium from this node (Hematoxylin and eosin stain original magnification ×8)

tion system could be traced electrophysiologically even in the presence of complete heart block

Our histologic observations demonstrate that the His bundle and the bundle branches were indeed located immediately underneath the recording sites Even prior to histologic verification the electrophysiological studies indicated that the His bundle in these two patients was *located in an unusual location superior* and anterior to the bulboventricular foramen rather than in the posteroinferior aspect of the defect[3] Because of this unusual location in which the specialized conduction system electrograms were recorded in our cases and because our histological studies indeed demonstrated the presence of specialized conduction system tissue at this site our findings verify the relationship between the location of the specialized conduction system and specialized conduction system electrograms obtained in the human patient

This correlation shows that specialized conduction system electrograms were indeed recorded at the location in which the specialized conduction system was found with histologic studies and clearly identifies for the surgeon the area of the specialized conduction system at risk

The current data are in accord with a recent electrophysiologic study from our group which showed that the amplitude of the specialized conduction system electrograms fell off sharply with distance and disappear within 2 to 3 mm

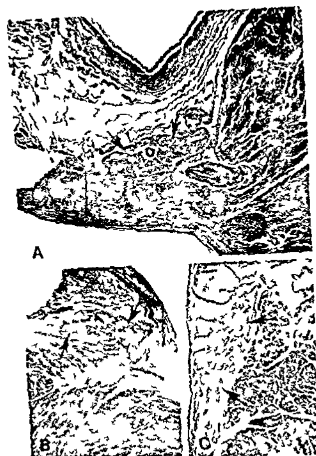


Fig 5 A through C A Anterior atrioventricular node (arrows) situated between atrial septum at its anterior junction with the atrial appendage and the pulmonary artery *B* Fibers of the anterior A V node were continuous with the atrioventricular bundle *(arrows)* which penetrated the fibrous ring *C* Continuity between the atrioventricular bundle and the specialized conducting syst m of the ventricle was traced through the fibrous ring adjacent to the pulmonary valve ring The His bundle *(arrows)* ran down the *right rim of the* bulboventricular foramen between the two chambers (Hematoxylin and eosin stain original magnification ×8)

from the recording probe The current study which demonstrates the relation between the histologic location of the His bundle and the locations from which specialized conduction system electrograms are recorded in man and the study by Dick and colleagues which describes the spatial behavior of these electrograms in man therefore prove that the intracardiac electrograms recorded either during open heart surgery or during cardiac catheterization originate in the specialized conduction system of the heart

Histologic studies describing the course of the specialized conduction system in patients with single ventricle and atrioventricular discordance have been recently described by Anderson and



Fig 6 A and B *A* At the level of the ventricular septum the left bundle branch continued into the main chamber and expands into a subendocardial network *(arrows)* *B* A cord like structure arises from the main bundle and transverses the foramen to the outlet chamber as a separate bundle of fibers In the outlet chamber *(arrows)* this bundle of fibers the right bundle branch rapidly expanded to form a subendocardial network (Hematoxylin and eosin stain original magnification ×11)

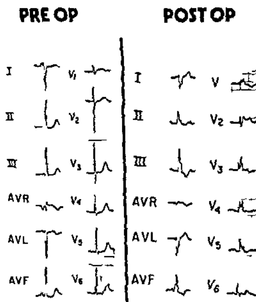


Fig 7 Preoperative and postoperative scalar el ctrocardiograms of the second patient Note complete A V block prior to and following surgery The *frontal* orientation of the *QRS* complex is +120 degrees and the QRS duration is 0 10 sec

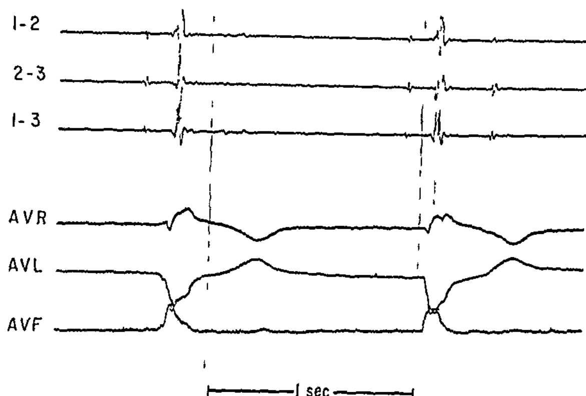


Fig 8 Intracardiac electrograms *(three upper panels)* and scalar electrocardiograms *(three lower panels)* of the second patient Note a His bundle electrogram preceding each QRS complex Note al o that the tracing was obtained in a patient with complete heart block

colleagues[9] and by Bharati and Lev [10] and concur with our observations In each patient the intra operative delineation was quite helpful to preserve the preoperative cardiac rhythm In one patient no injury to the specialized conduction system occurred during the division of the single chamber into two chambers and the patient maintained a normal sinus rhythm postopera tively In the second patient with complete heart block and junctional rhythm, prior to surgery the same heart rate and the same QRS duration and morphology were present postoperatively indi cating that no further damage occurred to the specialized conduction system during surgery

In most patients in whom intraoperative delin eation of the specialized conduction system is carried out the procedure is done during a supraventricular rhythm such as normal sinus rhythm or during atrial stimulation Such a supraventricular rhythm facilitates recognition of specialized conduction system electrograms which occur between the P and QRS complexes of the scalar electrocardiogram As shown however by our second case in some instances the location of the intraventricular parts of the specialized conduction system can be identified during complete heart block In addition to identifying the intraventricular parts of the specialized conduction system in patients with complete heart block and junctional rhythm we were able in the past to identify the specialized conduction system in patients with atrial fibrillation which occurs often during open heart surgery and precludes atrial pacing

Operative correction of Type A single ventricle has been previously reported for 23 pa tients[1 3 9 11 16] (Table I) Prior to the availability of specialized conduction system mapping proce dure six patients out of seven developed heart block following surgery (Table I), and one case[11] developed a transient heart block during surgery In contrast most previously reported patients who had electrophysiological delineation of their specialized conduction system did not develop heart block (Table I) [17]

Although the technique of placing sutures close to the specialized conduction system during normal sinus rhythm may be useful to prevent complete heart block transient injury and occa sional complete damage can nevertheless occur Since the location of the specialized conduction system can vary considerably [1] and many times the specialized conduction system can be visual ized following electrophysiologic identification

Table I Reported cases of primitive ventricle and outlet chamber (Type A) submitted for total operative repair

Number of cases with normal sinus rhythm	Reference	Intra operative mapping	Number developing postoperative heart block
1	1	no	1
2	5	no	2
1	9	no	1
1	11	no	1
2	12	no	2
1	13	yes	0
1	15	yes	0
24	16	yes	5
5	16	no	5
2†	Current report	yes	0

Temporary heart block which disappeared upon removal of sutures
†One case had heart block prior to operation but no further injury occurred to the specialized conduction system during the operation

we feel that this simple and brief technique should be employed in all centers in which congenital heart defects are being repaired

Summary

The specialized cardiac conduction system was delineated by electrophysiologic mapping during open heart surgery in two patients with single ventricle and levotransposition of the great arteries In both patients the conduction system was found to be superior and anterior to the bulboventricular foramen The sites where specialized conduction system electrograms were obtained were subsequently shown to contain the His bundle and the right and left bundle branches In one patient with congenital complete heart block the histologic studies demonstrated the site of block to be due to complete interruption of the His bundle The electrophysiologic–histologic correlation carried out in this study demonstrates the relationship between specialized conduction system electrograms obtained under direct vision during open heart surgery and the anatomic location of the specialized conduction system The study further supports the value of the electrophysiologic technique for intraoperative identification of the specialized conduction system and its reliability in cases where electrograms were obtained showing the specialized conduction system to be not in its anticipated location



Fig 9 A and B *A* The anterior atrioventricular node *(large arrow)* of the second patient with complete heart block was located between the atrial septum and the pulmonary artery This node gives rise to a beginning of an atrioventricular bundle *(small arrows)* however the bundle is rudimentary and ends before penetrating the fibrous ring No connection with the specialized conducting system of the ventricular septum could be traced either from the anterior or posterior atrioventricular nodes (Hematoxylin and eosin stain original magnification ×8) *B* On the ventricular aspect of the fibrous ring beneath the anterior atrioventricular node a bundle of specialized conducting tissue *(arrows)* was identified This bundle of fibers resembled the His bundle and branched into left and right bundle branches in similar fashion to the His bundle in Case 1 (Figs 5 and 6) However no connection to the anterior node was identified (Hematoxylin and eosin stain original magnification ×25)

The authors wish to thank Ms Sharon Kutner for her technical assistance

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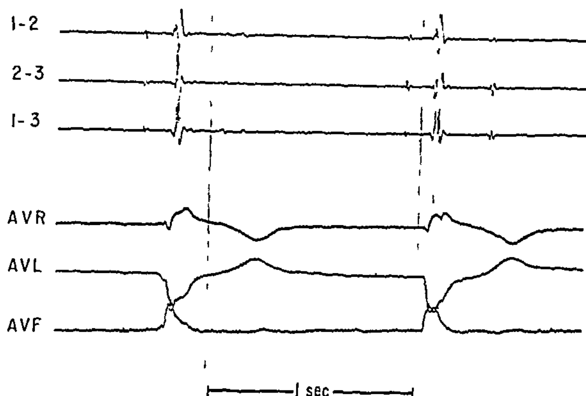


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Pleural effusion as a manifestation of Dressler s syndrome in the distant post infarction period

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Dresslers syndrome is a well recognized clinical entity which occurs in 3 to 4 per cent of patients following myocardial infarction[1] This syndrome usually develops within the first few weeks after infarction and is characterized by episodes of acute chest pain fever and pericarditis that tend to recur over many years During the initial episode of Dressler s syndrome pleural effusions are present in a high percentage of cases Although the development of a pleural effusion many months after infarction has been reported as the sole manifestation of this syndrome this clinical presentation is not well recognized We have recently evaluated a patient who presented with a bloody pleural effusion 2 ½ years after the initial onset of Dressler s syndrome Because of the therapeutic implications involved we are reporting this case to emphasize that pleural manifestations of this syndrome may occur in the distant post nfarction period

Case report

A 65 year-old white woman presented in January 1974 with an acute anterior myocardial infarction Forty-eight hours post infarction she complained of recurrent chest pain and a pericardial friction rub was noted This resol ed after 4 days without specific therapy

In May 1974 she was readmitted complaining of left lateral pleuritic chest pain She stated that the pain which was intermittent in nature would last for ? to 3 days and was associated with low grade fever She noted the presence of a non productive cough but denied hemoptysis There was no history of calf tenderness trauma or symptoms of other systemic diseases Her medications were digoxin chlorothiazide and spironolactone Positive physical findings included an oral temperature of 101 F., a pleural friction rub over the left lateral chest and a 3 component pericardial friction rub over the anterior chest An electrocardiogram showed diffuse ST segment elevation consistent with pericarditis and residual changes of an old anterior myocardial infarction A chest roentgenogram revealed blunting of both costophrenic angles Pleural fluid was not demonstrated on decubitus films A lung scan revealed no perfusion defects Lupus erythematosus preparations and antinuclear antibody studies were negative The patient s pain and fever responded to indomethacin and she was discharged after 6 days. However over the next 26 months she was admitted on five occasions for recurrence of the left sided chest pain A pericardial friction rub was present on two of these admissions On each occasion her symptoms resolved on indomethacin therapy

In September 19 6 she was admitted with complaints of dyspnea on exertion left pleuritic chest pain fever and a non productive cough At this time her medications were digoxin chlorothiazide and alpha methyldopa Physical examination revealed a well nourished white female in no acute distress She had an oral temperature of 101 F pulse of 90 beats per minute blood pressure of 150/9? mm Hg and a re piratory rate of 22/minute Cardiac examination was normal. Examination of the lungs revealed decreased tactile fremitus flatness to percussion and decreased breath sounds over the lower one third of the left hemithorax A coarse pleural friction rub was heard over this area A chest roentgenogram revealed a large left pleural effusion blunting of the right costophrenic angle and borderline cardiomegaly (Fig 1) An electrocardiogram showed evidence of the old anterior infarction Her routine laboratory studies were normal Serial studies for rheumatoid factor and antinuclear antibodies were negative Serum complement was within normal limits A thoracentesis yielded grossly bloody fluid Analysis of the fluid revealed 20 000 RBC/mm 1 800 WBC/mm (1 polymorphonuclear leucocyte 51 lymphocytes 9 monocytes, 37 large mononu clear cells) protein was 5 1 Gm per cent sugar was 139 mg

From the Pulmonary Dise se Servic U i ers ty Hosp t l, D p rt m t of Medicine Bost n Uni rsity School of Medicin

Received f public tion J ly 19 1977
Accepted for public t n A g 1 19"7

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Summary

A 65 year old woman developed a bloody pleural effusion 2 ¼ years after the onset of Dressler's syndrome Since an extensive evaluation failed to reveal a specific etiology the effusion was presumed to be a manifestation of Dressler's syndrome Because of the therapeutic implications involved we are reporting this case to emphasize that pleural effusions may occur as a manifestation of Dressler's Syndrome in the distant post infarction period

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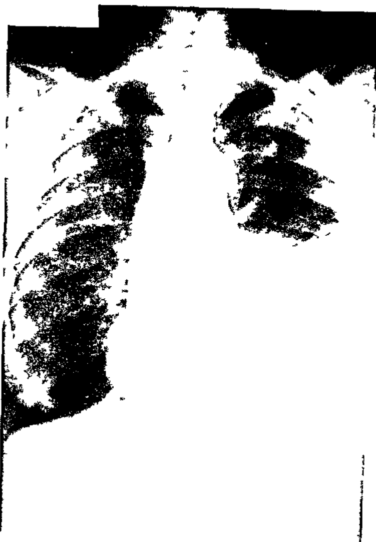


Fig 1 Chest roentgenogram obtained at the time of admission to the hospital in September 1976 revealing a left pleural effusion

per cent LDH was 705 I U amylase was 11 I U Pathologic examination of pleural biopsy specimens obtained on two different occasions showed changes of chronic inflammation Cell blocks and cultures of the pleural fluid were negative A tuberculin skin test (5 tu) was non reactive A perfusion lung scan revealed a non segmental defect in the area corresponding to the left sided pleural effusion A bronchoscopic examination was normal and washings yielded no abnormal cytologies A bone survey gallium scan and liver scan were all normal Methyldopa and hydrochlorothiazide were discontinued without effect

A tentative diagnosis of pleural effusion secondary to Dressler s syndrome was made The patient was treated with indomethacin with prompt resolution of her symptoms and a decrease in the amount of pleural fluid Because of gastrointestinal intolerance indomethacin was discontinued and the pain and pleural effusion recurred Institution of corticosteroid resulted in dramatic improvement in her symptoms and a decrease in the size of the effusion The patient has been followed for 9 months since the initial recognition of her bloody pleural effusion She has developed no evidence of an underlying malignancy connective tissue disorder or other systemic disease

Discussion

Although it is impossible to substantiate the diagnosis we feel that the bloody pleural effusion that developed in our patient was a manifestation of Dressler s syndrome The patient s history of recurrent chest pain and pericarditis over many months is characteristic of this syndrome Although the pleural effusion could have been caused by other diseases an extensive evaluation at the time of hospitalization and the subsequent period of follow up make it highly unlikely that the effusion was due to pulmonary infarction malignancy, infection drug reaction or systemic collagen vascular disease

Pleural effusions have been reported to occur in 68 to 88 per cent of the patients with Dresslers syndrome [1 2] The effusions are generally small and are unilateral in approximately 50 per cent of the cases Bloody pleural effusions are distinctly uncommon Of the 35 effusions in Dresslers series only three were hemorrhagic and one of these appeared to be a direct complication of anticoagulant therapy Gelfand and Effros[3] reported an additional case of a bloody pleural effusion in Dressler's syndrome but the patient in this report was also receiving anticoagulants Although the majority of patients with this syndrome have pericarditis it is well recognized that clinical evidence of pericardial disease may not be present at the time pulmonary manifestations are apparent

In the absence of pericardial disease the development of a pleural effusion in a patient with Dressler s syndrome presents a difficult diagnostic problem since as in our case more common etiologies of pleural effusion must be considered [4] Nevertheless it is important to be aware of the fact that isolated pleural effusions may occur in Dressler s syndrome since hemopericardium and cardiac tamponade have occurred in patients with this syndrome who were anticoagulated Thus in a patient who has had prior manifestations of Dressler s syndrome and who develops a pleural effusion the diagnosis of pulmonary infarction must be carefully documented prior to the institution of anticoagulant therapy The possibility that the effusion represents a manifestation of Dressler s syndrome should be considered In this event the majority of these patients will respond dramatically to corticosteroids although salicylates or indomethacin may also be effective

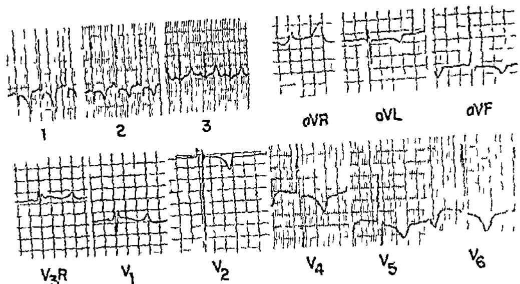


Fig 2 Chest radiograph taken 1 month before death showing marked cardiac enlargement



Fig 3 Frames from left ventricular angiogram in end systole *(left)* and diastole *(right)* The left ventricular wall is markedly thickened and the left ventricular cavity is not dilated

heart failure Shortly after admission cardiac catheterization was performed and showed the following pressures in mm of mercury in the right atrium (mean) 4 right ventricle 20/3 pulmonary artery 21/5 with a mean of 11 left atrium (mean) 11 left ventricle 65/7 No gradient was demonstrated across the left ventricular outflow tract Cardiac output was 0 8 liters/minute left ventricular stroke volume was 5 1 ml which was 30 per cent above the predicted value for height and weight Systemic and pulmonary vascular resistance were low Right and left ventricular angiograms showed thickened ventricular walls and interventricular septum normally related ventricular cavities and great vessels and a left ventricular ejection fraction of 70 per cent (Fig 3) No coronary artery anomalies intracardiac shunts or valvular regurgitation or stenosis could be demonstrated Echocardiogram (Fig 4) demonstrated symmetrical left ventricular hypertrophy without ventricular cavity enlargement Thallium 201 myocardial perfusion imaging showed homogenous tracer uptake without focal defects a markedly thickened non

Clinical pathologic conference

Pompe's disease presenting as hypertrophic myocardiopathy with Wolff-Parkinson-White syndrome

Bernadine H. Bulkley, M.D.
Grover M. Hutchins, M.D.
Baltimore, Md.

Clinical summary

A 5-month-old white female was the offspring of a consanguineous mating between her 17-year-old mentally retarded mother and the mother's 61-year-old maternal grandfather. After an uneventful pregnancy and delivery the child exhibited unexplained irritability and poor feeding. Continued failure to thrive was noted after discharge home and by age 2 months a precordial murmur and cardiomegaly were noted and she was admitted to the hospital for evaluation.

On examination she was an alert, irritable, thin infant with circumoral cyanosis. Length, weight, and head circumference were at the 3rd percentile for age. Pulse rate was 140 per minute and regular, respirations were 45 per minute, and blood pressure was 95 mm. Hg by palpation. Pertinent physical findings included and enlarged tongue and clear lungs and a Grade 2/6 harsh systolic ejection type murmur over the aortic area. There were no heaves, thrills, or precordial bulges and the left ventricular impulse was displaced laterally. The liver extended 2 cm. below the right costal margin. Firm prominent musculature was noted in all extremities but muscle tone was diminished and strength poor.

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Supported by Grant P50-HL-1[illegible] with The National Institutes of Health, Public Health Service, Department of Health, Education and Welfare and the Sadler Research Fund for Women Physicians.

Received for publication May 9, 19[illegible]

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Fig. 1. Electrocardiogram taken at age 3 months showing short PR interval, left ventricular hypertrophy, and the suggestion of a delta wave in aVF and V_1. The heart rate was 1[illegible]0; the paper speed has been increased to 50 mm./sec. in aVR, aVL, and aVF and in the precordial leads.

Laboratory studies showed a hematocrit of 37, white blood count 18,600, serum potassium of 6.0 mEq./mL., with other serum electrolytes normal, and serum glucose of 120 mEq./ml. Chest radiograph (Fig. 1) showed cardiomegaly with a cardiothoracic ratio of 0.7, a left aortic arch and normal pulmonary vasculature. Electrocardiogram showed a short PR interval (0.08) and left ventricular hypertrophy and possible subendocardial ischemia (Fig. 2). Arterial blood gasses on 40 per cent inspired oxygen were as follows: Po 61 mm. H O, Pco 43, pH 7.37. Serum creatinine phosphokinase was elevated to 17[illegible]0 with a positive MB fraction, raising the possibility of myocardial infarction as a cause of her obscure congestive

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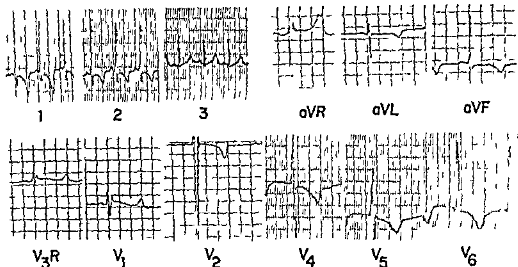


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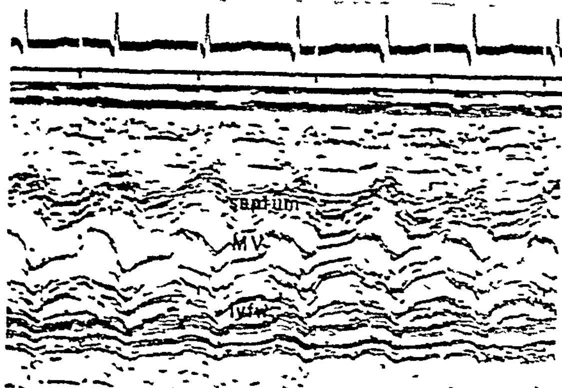


Fig 4 Echocardiogram showing small left ventricular cavity and good wall motion. The decreased E to F slope of the mitral valve (MV) is compatible with diminished left ventricular compliance associated with severe left ventricular hypertrophy *lvfw* = left ventricular free wall.

dilated left ventricle without asymmetric septal hypertrophy gated cardiac blood pool scan *demonstrated an ejection fraction of in excess of* 70 per cent and no segmental wall motion abnormalities.

Treatment with digitalis and diuretics failed to improve her heart failure Because of the results of both invasive and noninvasive studies showing hyperdynamic hypercontractile heart digitalis was discontinued and propranolol instituted with demonstrated improvement Because of tongue and skeletal muscle abnormalities skeletal muscle biopsy was performed and revealed changes compatible with glycogen storage disease

The child was discharged home but continued to do poorly failing to gain weight and continuing to have episodes of cyanosis and irritability On frequent outpatient visits she remained relatively unchanged although by chest radiograph her heart continued to enlarge Without warning at five months of age she died suddenly at home

Discussion

DR. BERNADINE H BULKLEY This 5 month old female was unwell from the time of birth Initially she showed nonspecific signs of poor feeding and irritability The cause of her failure to thrive did not become apparent however until 2 *months of age when she was noted to have a heart* murmur and unexplained cardiomegaly Echocardiogram suggested left ventricular hypertrophy without evidence of asymmetric septal hypertrophy and Thallium 201 myocardial perfusion imaging which may also be a useful noninvasive method for detection of asymmetric septal hypertrophy [1] showed only concentric hypertrophy with a normal to small sized left ventricular cavity Cardiac catheterization revealed essentially normal right and left ventricular pressures and no evidence of intracardiac shunting valve abnormalities, or congenital malformation She did have an increased stroke volume for size and an increased ejection fraction of 70 per cent suggesting a hypertrophic cardiomyopathy Bi ventricular angiograms also showed ventricular *hypertrophy and a small left ventricular cavity*

Thus, congenital aortic stenosis or atresia were ruled out by the catheterization studies, as was the possibility of an anomalous left coronary artery which might have been suggested by the elevated cardiac enzymes. The lack of ventricular dilatation and good ventricular function elimi

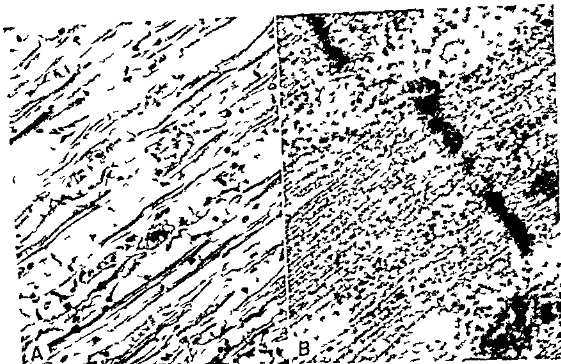


Fig 5 A and B A Histological section of skeletal muscle biopsy showing marked vacuolization of muscle fibers by glycogen deposits There is considerable variation in fiber size (Hematoxylin and eosin stain original magnification ×300) B Electron micrograph of skeletal muscle showing extensive granular glycogen deposits between the myofilaments (original magnification ×63 000)

nated viral myocarditis or endocardial fibroelastosis from consideration Her clinical findings were most compatible with a hypertrophic cardiomyopathy a condition which infrequently presents this early in life Features of her presentation that led to the precise diagnosis were largely extracardiac By physical examination she had a noticeably enlarged tongue and her skeletal muscle in all four extremities was firm prominent but also weak with poor tone Also her liver was enlarged The best explanation for the large tongue hepatomegaly hypotonia and cardiomegaly was glycogen storage disease Other myopathies that may affect skeletal muscle such as Duchenne's muscular dystrophy either do not present this early in life or do not have the degree of cardiac involvement

Dr Hutchins will you describe the findings on skeletal muscle biopsy?

DR GROVER M HUTCHINS The skeletal muscle pathology was quite typical of Type II glycogen storage disease The muscle fibers are all distended by sarcoplasmic accumulations of glycogen (Fig 5) By analysis the tissue had 9 3 Gm per cent glycogen compared to normal levels of less than 1 5 Gm per cent Furthermore absence of the enzyme of α1 4 glycosidase was shown by assay

The accumulation of massive quantities of normal glycogen in certain tissues of patients with Type II glycogenosis or Pompe's disease appears to be explained by deficiency of the lysosomal enzyme capable of degrading the glycogen molecule The normal metabolic pathways of glucose utilization are intact however so that energy productivity by the cell is unimpaired

The lysosomal acid maltase is absent in not only cardiac and skeletal muscle but also in leukocytes fibroblasts and cells of the liver and central nervous system Diagnosis can be made by demonstrating the enzyme deficiency in leukocytes but the most definitive diagnosis technique is muscle biopsy with glycogen quantitation

DR BULKLEY Type II glycogen storage disease carries a grave prognosis with most infants dying of cardiac involvement within the first year of life [7] There have been unsuccessful attempts to treat these infants with enzyme infusions[1] and to date treatment is only symptomatic This child

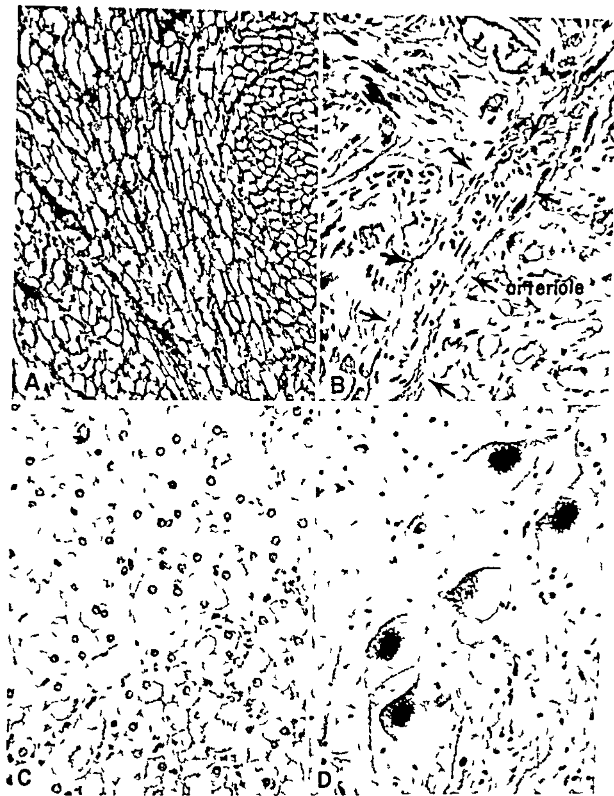


Fig 6 A through D Histology of tissues obtained from autopsy *A* Myocardium with marked vacuolization of cardiac muscle cells (Periodic acid Schiff stain original magnification ×150) *B* Striated muscle of tongue with distortion and vacuolization of muscle cells by sarcoplasmic glycogen accumulation The media of arterioles *(arrow)* also shows vacuolization of smooth muscle cells by glycogen accumulation (Hematoxylin and eosin stain original magnification ×300) *C* Liver with hepatocytes distended by glycogen deposits (Hematoxylin and eosin stain original magnification ×400) *D* Spinal cord anterior horn with motor neurons containing glycogen (Hematoxylin and eosin stain original magnification ×300)

deteriorated on digitalis as is true of hypertrophic myocardiopathy, and was improved with propranolol therapy Over the last 3 months of her life however, she showed progressive cardiomegaly and finally died suddenly at home

Dr Hutchins would you describe the autopsy findings?

Dr Hutchins The body was small for a 5 month old infant weighing only 3 kilograms and being 55 cm in length The musculature was

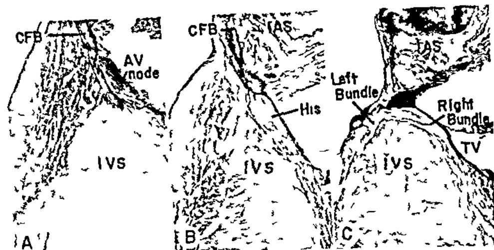


Fig 7 A through C Selected serial histological sections of the atrioventricular node and bundles. Sections are viewed with right side on right and interatrial septum at top *A* At level of atrioventricular *(AV)* node which is on the atrial side of the central fibrous body *(CFB)* *B* Slightly further along the conducting pathways the poorly defined His bundle establishes contact with the right ventricular septal muscle *IAS* = interatrial septum *IVS* = interventricular septum *C* The left bundle arises more distally in the conducting system *TV* = tricuspid valve (All periodic acid Schiff stain original magnification ×10)

prominent especially in the tongue and diaphragm The heart was markedly enlarged weighing 88 grams as compared to an expected weight of approximately 26 grams Despite the over all increase in heart size the chambers were all of about normal volume and the valve diameters were appropriate for the over all body size The myocardium was greatly thickened in all chambers as a result of the same glycogenic accumulation as seen in the skeletal muscles (Fig 6) Extensive glycogen accumulation was present in the working myocardium of all four cardiac chambers There was no histologic evidence of myocardial necrosis or fibrosis and the coronary arteries were normal

The other organs were grossly unremarkable The lungs had severe congestion and edema No other cause of death could be found Glycogen demonstrated by comparison of periodic acid Schiff stains with and without diastase digestion was found especially in the liver skeletal muscle smooth muscle and in neurons of both the central and peripheral nervous system (Fig 6) It is possible that the skeletal muscle weakness in these patients relates to neuronal glycogenosis

The autopsy findings in this patient are typical of Type II glycogen storage disease the only one of the several disorders of glycogen accumulation associated with specific enzyme defects that significantly affects cardiac function

DR. BULKLEY Pompe s disease is a rare disorder that appears to have an autosomal recessive pattern of inheritance No more than 50 or 60 cases have been reported in the literature most of them having limited clinical and pathologic evaluation Comparing our patient with three previously reported[3-5] in whom cardiac catheterization had been performed during life the clinical illnesses appear remarkably similar Each of the infants presented with a general failure to thrive and had idiopathic left ventricular hypertrophy short PR intervals on electrocardiogram and at catheterization had hyperdynamic cardiac function In one of these reported patients[3] outflow tract gradients could be provoked suggesting an obstructive form of hypertrophic disease The similarity of these patients to those with familial idiopathic hypertrophic subaortic stenosis associated with asymmetric septal hypertrophy[6] points out the heterogeneous spectrum of disease which falls within the category of hypertrophic cardiomyopathy[7] These patients also point out the nonspecificity of most of the findings associated with hypertrophic states with or without gradients at catheterization all hypertrophic cardiomyopathies are clearly not associated with asymmetric septal hypertrophy and abnormal myocardial fiber arrangement

Another interesting aspect of the cardiac disorder of Pompe s disease is the occurrence of a pre excitation syndrome Wolff Parkinson White syndrome (WPW) has been associated with a variety of congenital disorders including Ebstein s

anomaly, atrial septal defect, ventricular septal defect and tetralogy of Fallot[15] In addition familial hypertrophic cardiomyopathy is not infrequently associated with Wolff Parkinson White syndrome[17] The abnormal ECG in this infant was compatible with a number of congenital lesions and with hypertrophic cardiomyopathy or Pompe's disease

Pre excitation syndromes are generally believed to result from an accessory atrioventricular myocardial pathway which is separate from and bypasses, the AV node and bundle of His Accessory pathways are generally believed to cross the posterior and lateral wall of the atrioventricular groove but some may be located more centrally near the atrioventricular node[1 18] Although a pre excitation syndrome has been described in Pompe's disease, there is little or no information about the morphology of the conduction system in this disease Dr Hutchins did you study the conduction system in this infant?

Dr Hutchins The conduction system in this child was of great interest at autopsy and serial histological sections of the sinoatrial node and atrioventricular (AV) node His bundle and bundle branches were performed Glycogen accumulation was present in the specialized conduction tissues as in the working myocardium In addition the anatomy of the atrioventricular node His bundle and bundle branches was unusual (Fig 7) The His bundle was remarkably ill defined The AV node penetrated the central fibrous body at a more proximal level than usual and within a few hundred microns gave rise to a large right bundle connecting directly with the myocardium of the interventricular septum The fascicles of the left bundle arose at a more distal level Thus the pre excitation in this infant appears to be explained by a centrally located abnormality within the AV node and His bundle per se

Dr Bulkley In summary this unfortunate infant offspring of a consanguineous union was born with a recessively inherited metabolic disease which lead to her death by 5 months of age Although she had increased and progressive glycogen deposition in most of the tissues of her body, it was the cardiac involvement that caused most of her clinical illness and death

There are at least eight different forms of inherited diseases of glycogen metabolism that are now recognized which form a broad spectrum of clinical illness Type II glycogen storage disease, the only one to extensively involve the heart, carries one of the bleakest outlooks

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Fundamentals of clinical cardiology

Mitral valve repair for significant mitral insufficiency

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Prior to the article by Starr and Edwards in 1961[1] on mitral valve replacement it was necessary to repair the abnormally functioning mitral valve at the time of surgery since a prosthetic mitral valve was not available With the introduction of prosthetic valves it has been technically easier for surgeons to replace the valve than attempt repair Our first repair for pure mitral insufficiency was performed in 1959 and except for brief periods this has remained our method of choice for surgery for significant mitral insufficiency for the past 18 years Repair has not been popular with surgeons however since repair is more difficult and takes greater thought than excising a valve and replacing it with a prosthesis With 15 years clinical and experimental experience with various prosthetic devices it is our strong conviction that a mitral prosthesis of any variety or a porcine valve should be inserted only if repair cannot be accomplished

With short and long term results of mitral valve replacement being published not only with the Starr Edwards valve but also the Hancock porcine valve it would appear of interest to compare these results to the results with repair of the insufficient mitral valve The following is a report of two groups of patients 145 patients with pure mitral insufficiency in whom mitral repair was performed from 1959 to 1977 and 55 patients with mitral insufficiency and coronary artery disease in whom repair was performed at the time of myocardial revascularization from 1970 to 1977

Although the basic principle is the same for repair of the insufficient mitral valve for all patients the data from the two groups of patients is presented separately in this article

Since 1970 myocardial revascularization has been performed in all but one patient with mitral insufficiency and coronary artery disease requiring mitral valve surgery when significant coronary artery disease was present In this patient revascularization was not needed nor possible since the vessel obstructed led to an area of infarct and the other two vessels had only minimal disease These patients comprise Group II There were 14 patients operated upon prior to 1970 with mitral insufficiency and coronary artery disease but myocardial revascularization was not combined with repair or replacement by us until 1970 These patients are included in the first group of patients with pure mitral insufficiency There may be other patients in Group I who had coronary artery disease and whose mitral insufficiency was due to or associated with the coronary artery disease and were operated upon for their mitral insufficiency during the years from 1959 If so the coronary artery disease was not proven even though suspected since coronary arteriography was not performed in these patients

In order to better understand our approach to

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Aided by a grant from The Los Angeles Thoracic and Cardiovascular Foundation.

Received for publication Dec 1, 19 7

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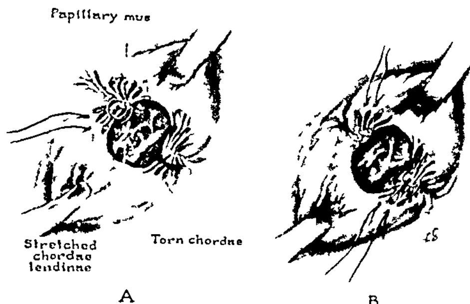


Fig 1 The area of the leaflet involved with stretched or torn chordae tendineae or torn papillary muscle is repaired by placing interrupted figure of eight sutures of 2 0 Tevdek through the head of the nearer papillary muscle and then bringing this suture up through the leading edge of the involved area of the leaflet Usually two separate sutures are used at each area For ease of exposure all sutures are placed prior to tying

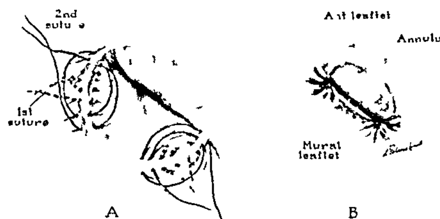


Fig 2 In order to obliterate the insufficiency the greatly dilated sagging mural annulus is decreased considerably in size This must be accomplished by decreasing the length of the mural annulus to about ½ of its size and thereby bringing it up into apposition with the anterior leaflet The annulus of the anterior leaflet cannot be encroached upon *The repair is accomplished with No 2 silk sutures as illustrated*

the repair of the mitral valve it is important to be familiar with our thinking as to the development of mitral insufficiency Whether the patient began with mitral valve prolapse without significant insufficiency and over the years developed wide open mitral insufficiency or whether the patient had myocarditis and developed mitral insufficiency secondary to this the progression is similar With mitral valve prolapse the annulus is large and the leaflets meet only at their edges With myocarditis the left ventricle enlarges thereby enlarging the annulus and the mitral leaflets do not coapt Because the leaflets meet only at their edges or not at all there is significant tension on the leaflets each time the heart contracts This creates tension on the chordae tendineae as well With time the leaflets stretch and enlarge as do the chordae tendineae In many patients the chordae tendineae tear The leaflets are usually thickened and reveal fibromyxoid degeneration This fibromyxoid degeneration in the leaflets is secondary to the trauma produced by the pressure of the blood on the unsupported leaflets during systole

With mitral insufficiency secondary to coronary artery disease the mitral insufficiency may be due to tearing of infarcted papillary muscle or

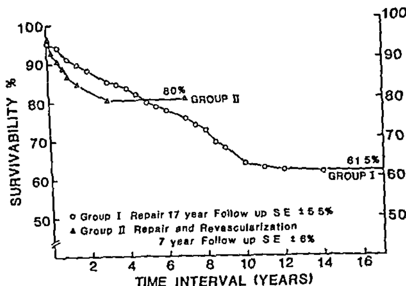


Fig 3 Actuarial curves Mitral repair results for Group I and Group II patients using Biomedical Computer Program BMD11S

chordae tendineae because of infarcted papillary muscle With these patients there is always secondary annular dilatation due to enlargement of the left ventricle In other patients with coronary artery disease the infarct may involve the muscle near the annulus with resultant dilatation of the annulus and failure of coaptation of the leaflets In some patients with a massive infarct the annulus may be stretched due to enlargement of the left ventricle

No matter what the etiology of the mitral insufficiency it is always necessary to decrease the size of the annulus and this part of the repair is almost always performed in the same manner This consists of decreasing the length of the mural annulus and not the annulus of the anterior leaflet The trigona fibrosa cordis prevents the annulus of the anterior leaflet of the mitral valve from stretching The mural leaflet portion of the annulus does not have a similar support and therefore the mitral annulus dilates at the area of the mural annulus but not the area of the anterior annulus It is important to remember that the mural annulus only is stretched in all patients with mitral insufficiency

The majority of patients with mitral insufficiency not secondary to coronary artery disease will have torn chordae tendineae and/or stretched chordae tendineae The patient with mitral insufficiency secondary to myocardial infarction may or may not have torn chordae tendineae or torn papillary muscle but they will not have associated stretched chordae tendineae unless the insufficiency is of many years duration

Technique

The technique of repair is as follows After opening the left atrium a careful search is made to determine if there are torn or stretched chordae tendineae or torn papillary muscle If there are significantly stretched chordae tendineae torn chordae tendineae or torn papillary muscle this area of the valve is sutured down to the nearest papillary muscle head (Fig 1) New chordae are not constructed The anterolateral posteromedial, midportion or all three areas of the mural leaflet may require suturing to the nearest papillary muscle If there are torn or stretched chordae tendineae of the anterior leaflet this area is sutured to the head of the papillary muscle involved If all of the chordae tendineae of the anterior leaflet are stretched then either the anterolateral or posteromedial portion of the anterior leaflet is sutured to the head of the nearest area involved (Fig 1) This allows the remaining portion of the anterior leaflet to billow and close against the mural leaflet It is important for the anterior leaflet to billow in order to abut against the mural leaflet otherwise the insufficiency will not be corrected

Except for minor variations in individual

Table I Mitral insufficiency without myocardial revascularization—repair failures

Patient No	Age at first surgery	Date of first surgery	Initial cause of mitral insufficiency	Cause of failure	Date of subsequent surgery	Procedure	Outcome
1	R F 36	8/11/59	Torn chordae tendineae of anterior leaflet	Torn chordae *not* repaired at initial operation	10/1/63	Replacement with No 3 Starr Edwards Ball valve 4 yrs later	Ball valve replaced 11 years later for valve thrombosis
				Thrombosis of Starr valve	9/27/74	Replacement with No 31 Hancock glutaraldehyde porcine valve 11 yrs later	Living and well on Coumadin 3 yrs
2	G P 37	9/2/60	Dilated annulus prolapsed anterior leaflet with stretched chordae tendineae	Stenosis with calcification of area of previous repair	7/11/74	Replacement with No 29 Hancock glutaraldehyde porcine valve 14 yrs later	CVA 3 yrs after insertion of porcine valve Living and well 3 yrs on Coumadin
3	M P 48	10/31/61	Cross dilatation due to stretched C T mural & anterior leaflet	Torn C T anterior leaflet greatly dilated tricuspid annulus with insufficiency	12/10/70	Second repair of mitral valve and primary repair of tricuspid valve 9 yrs later	Living and well 7 yrs no murmurs or medication
4	J P 37	5/19/64	Dilated annulus with calcification slightly stretched C T	Stenosis due to calcification of both leaflets	9/9/76	Replacement with No 31 Hancock glutaraldehyde porcine valve 12 yrs later	Living and well 1 year on Coumadin
5	P C 39	7/29/66	Torn C T mural leaflet	Recurrence of torn chordae tendineae	1/17/68	Replacement with No 4 Kay Shiley disc valve Tricuspid annuloplasty 2 yrs later	Living and well 9 5 years on Coumadin
6	T D A 47	9/8/67	Torn C T mural leaflet	Repair of mural leaflet intact Torn C T occurred at anterior leaflet	10/8/73	Replacement with No 7 Kay Shiley disc valve with muscle guard 6 yrs later	Hosp death Bronchial pneumonia probable myocardial infarction

patients the remaining part of the mitral valve repair is now the same for all patients and consists of decreasing the annulus of the mitral valve by doing away with approximately 65 per cent to 70 per cent of the annulus of the mural leaflet The annulus is decreased mainly at the posteromedial commissural area where usually two interrupted figure of eight sutures of No 2 silk are placed and tied to do away with 40 per cent or 45 per cent of the annulus The same procedure is used to decrease the mural annulus of the anterolateral commissural area for another 20 per cent or 25 per cent The sutures placed at the anterolateral commissural area should not be deep so that the circumflex coronary artery is encircled When the annuloplasty is completed approximately 30 per cent or 35 per cent of the mural annulus remains and there is a snug two fingerbreadth opening (Fig 2) *It is important not to encroach on the annulus of the anterior leaflet,*

Table I continued

Patient No	Age at first surgery	Date of first surgery	Initial cause of mitral insufficiency	Cause of failure	Date of subsequent surgery	Procedure	Outcome
7	M T 61	10/1/68	Calcification mural leaflet Prolapse of both leaflets	Mitral insuff due to large anterior leaflet with stretched C T	5/10/76	Second mitral valve repair 8 yrs later	Living and well 1 year no medication no murmur
8	J G 66	11/26/68	Torn C T mural leaflet	Prolapse of anterior leaflet due to stretched C T	5/27/69	Replacement with No 8 Kay Shiley disc valve with muscle guard 1 yr later	Died 6 months after surgery Cause unknown
9	J G 59	1/9/69	Torn C T mural leaflet	Mitral insuff through center of repaired valve	2/20/6[illegible]	Replacement with No 8 Kay Shiley disc valve with muscle guard 1 month later	Lost to follow up
10	G B 47	[illegible]	Torn C T mural leaflet	Mitral insuf due to tear of suture line	10/7/71	Replacement with No 7 Kay Shiley disc valve with muscle guard	Living and well 6 years on Coumadin
11	E L 5[illegible]	6/24/74	Torn C T mural leaflet stretched C T anterior leaflet S B E 6 yrs prior to surgery	Torn C T anterior leaflet	6/16/75	Replacement with No 31 Hancock glutaraldehyde porcine valve 1 yr later	On Coumadin & aspirin Emboli causing temp blindness after valve replaced living 2 years
12	D C 6	1[illegible] 9/74	Dilated annulus with stretched C T coarctation & aortic aneurysmectomy 20 years previously	Mitral insuf due to prolapsed anterior leaflet	4/3/7[illegible]	Replacement with No 31 Hancock glutaraldehyde porcine valve 4 months later	Living and well 2 years on Coumadin

otherwise mitral stenosis may be produced without correcting the insufficiency This technique was first described in 1961 and in subsequent publications

Material

Group I—Mitral insufficiency without myocardial revascularization Between 1959 and 1977 216 patients were operated upon with significant pure mitral insufficiency The majority of these patients had mitral valve prolapse with severe insufficiency and without coronary artery disease Mitral valve repair was performed in 145 patients (67 per cent) and replacement was performed in 71 (33 per cent) Ages varied from 17 to 76 years in these patients There were 80 men and 65 women followed from 6 months to 17 years after surgery Thirty eight were in New York Heart Association Class IV and 107 were in Class III Nine patients (6 per cent) had a myocardial infarct 15 days to 84 months (mean 18 months) before surgery Six of these nine patients had angina at the time of surgery Five more patients (3 per cent) had angina preoperatively but had not had an infarct In 68 patients (47 per cent) a history of rheumatic heart disease and in 10 patients (47 per cent) a history of subacute bacterial endocarditis had been noted The heart size as demonstrated by x ray ranged from Grade 2/6 to 5/6 enlarged with a mean of 3/6 Seventy three patients had torn chordae tendineae and 15 had a ruptured infarcted or necrotic head of a

papillary muscle In 26 patients there were stretched chordae tendineae and in the remaining 31 patients the operative report mentioned only a dilated annulus Prior to performing repair a portion of the valve was removed for biopsy in 29 patients Fibromyxoid degeneration of the mitral leaflet was noted in 19 patients inactive rheumatic changes in seven patients and valvulitis of the valve with calcification in three patients These pathological findings were essentially the same as in those patients in whom the excised valve was replaced

Group II—Mitral insufficiency and myocardial revascularization From 1970 to 1977 67 patients were operated upon with myocardial revascularization and mitral repair of replacement In 57 patients mitral insufficiency occurred secondary to coronary artery disease and in 10 the patient's knowledge of mitral insufficiency antedated the history of coronary artery disease Repair was feasible in 55 of these patients (82 per cent) Of these 55 patients undergoing repair 19 were women and 36 were men between 12 and 72 years of age (mean 59) Twenty seven patients were in New York Heart Association Class III and 28 were in Class IV The patients were classified on the basis of fatigue dyspnea and congestive heart failure These symptoms were accompanied by angina in 46 patients, but severity of angina was not used for classification Eleven patients had Grade II/VI 26 had Grade III/VI and 18 Grade IV/VI mitral insufficiency The amount of insufficiency was determined as follows The cardiac output was obtained by the Fick Principle The stroke volume of the left ventricle was determined by radiographic means with injection of 76 per cent Renografin into the left ventricle If the amount of blood ejected into the left atrium equaled that ejected into the aorta then this was graded as II/VI If the blood ejected into the left atrium was two times the amount ejected into the aorta this was Grade IV/VI If the amount ejected into the left atrium was three times the amount ejected into the aorta this was graded as VI/VI

The pulmonary artery pressure was measured prior to left ventriculography and coronary arteriography in 27 patients These varied from a normal of 24/13 to a high of 119/61 with 16 patients (59 per cent) having a pulmonary artery systolic pressure of 50 mm Hg or more The left ventricular end diastolic pressure prior to radiopaque studies was measured in 35 patients and varied from 7 mm Hg to 38 Twenty nine patients (83 per cent) had an end diastolic pressure of 15 mm Hg (mean 22 6) or greater The ejection fraction was also measured prior to coronary arteriography and ranged from 0 15 to 0 7 in these 55 patients

Thirty three patients had a ruptured or infarcted papillary muscle or torn chordae tendineae with secondary annular dilatation Twenty two patients had a dilated annulus only At operation 92 vein grafts and six left internal mammary arteries were employed for myocardial revascularization

Results

Group I There were 7 hospital deaths (5 per cent) in the 145 patients with mitral valve repair Repair failed in 12 patients (8 per cent) from 1 month to 14 years (mean 4 6 years) after the initial operation Table I Two of these patients had a second repair 7½ and 8¼ years after the first operation and both are doing well without a murmur 1 and 7 years following the second operation In one of these two patients tricuspid repair as described in 1965[11,1] was also successfully performed at the time of the second operation Of the 10 patients with subsequent valve replacement seven patients are alive 9 months to 9½ years after mitral valve replacement

There were 30 (20 per cent) late deaths from 3 months to 10 years (mean 5 years) after mitral valve repair Table II Two of the 30 late deaths were due to hepatitis 12 were due to myocardial infarction, and six deaths were due to carcinoma or leukemia Thromboembolic events occurred in four patients followed for a total of 922 years 0 4 per cent per patient year These four emboli resulted in the hospital death in one patient and late death in two patients The fourth patient had a cerebral vascular accident 2½ years after mitral repair from which he recovered completely but died 6½ years later The autopsy revealed a recent myocardial infarct with pulmonary emboli Change in the New York Heart Association classification as judged by a physician is noted in Table III The actuarial curve revealed a survivability of 61 5% (±5 5%) at 17 years (Fig 3) Of the 10 patients with subsequent valve replacement one is lost to follow up and seven patients are

Table II Mitral insufficiency without myocardial revascularization—late deaths

No of patients	*Cause of death*	*Time postoperative*
1	Serum hepatitis	5 mos
1	Infectious hepatitis	7 yrs
1	Myocardial infarction	3 mos to 9½ yrs
1	Suicide	1 yr
2	Lung carcinoma	1½ and 10 yrs
	Stroke	1½ and 5 yrs
2	Breast carcinoma	8 and 1[illegible] yrs
1	Intestinal cancer	[illegible] yrs
	Pulmonary embolus (1 myocardial inf)	3½ and 6½ yrs
1	Ventricular fibrillation	1 [illegible] yr
1	Leukemia	5 yrs
4	Unknown	4 yrs to 9 yrs

alive from 1 to 9½ years with a survivability of 73.6 per cent (±16%) at 9 years

Group II There were two (4 per cent) hospital deaths in these 55 patients One patient with an ejection fraction of 0.2 died of bacterial endocarditis 37 days following surgery and one patient with an ejection fraction of 0.4 died 8 days after surgery of a pulmonary embolus Table IV reveals the hospital deaths and late deaths as related to the ejection fraction and Table V lists the cause of the six late deaths Table VI reveals the postoperative change in New York Heart Association Classification of the 47 surviving patients The survivability at 7 years is 80% ± 6% (Fig 3)

There was one peripheral embolic event resulting in hemiplegia in the 55 patients with repair followed for a total of 164 years or 0.6 per cent per patient year One patient with repair died from cerebral hemorrhage 7 months after surgery however this patient was continued on sodium warfarin by her family physician for 7 months at which time she had a cerebral hemorrhage with the prothrombin time at 10 per cent Anticoagulant therapy is advised for only 3 months following mitral repair with the prothrombin time maintained at 20 per cent

Discussion

Patients with mitral insufficiency should be operated upon if with adequate medical therapy their symptoms prevent them from performing their daily duties in a manner satisfactory to the

Table III Mitral insufficiency without myocardial revascularization—NYHA functional classification of 96 surviving patients

	Total postoperative class			
	IV	*III*	*II*	*I*
Preoperative class IV		1	11	17
III			2	4
II				
I				

Table IV Preoperative ejection fraction as related to mortality in patients with mitral repair and myocardial revascularization

	Ejection fraction		
	0.15-0.20	*0.25-0.40*	*0.41-0.[illegible]*
Total patients	4	23	27
Hospital deaths	1	1	0
Late deaths	2	1	3
Total deaths	3 ([illegible])	2 (9%)	3 (11%)

patient Because of the increased morbidity with mitral valve prostheses it is imperative that mitral valve repair be considered before replacement Few surgeons however are presently prepared to attempt repair for mitral insufficiency In 1976 Salomon Stinson Griepp and Shumway reported on 66 patients with pure mitral insufficiency without coronary artery disease This group of patients is similar to our 145 patients with pure mitral insufficiency in whom repair was performed The mitral valve was replaced in their 66 patients Starr Edwards Model 6120 valves were used in 38 patients porcine aortic valve Xenografts (Hancock) in 20 and stented aortic valve allografts in eight The operative mortality rate was 6 per cent The overall survival rate calculated by the actuarial method was 50 per cent ± 8 per cent at five years Ten of their 38 operative patients with the Starr Edwards valve inserted in the mitral area had systemic thromboembolic episodes with two deaths from the emboli Two of their eight patients with an allograft in the mitral area had systemic thromboembolic episodes None of the patients with the porcine valve had systemic thromboembolic episodes at the time of this

papillary muscle In 26 patients there were stretched chordae tendineae and in the remaining 31 patients the *operative report mentioned* only a dilated annulus Prior to performing repair, a portion of the valve was removed for biopsy in 29 patients Fibromyxoid degeneration of the mitral leaflet was noted in 19 patients inactive rheumatic changes in seven patients and valvulitis of the valve with calcification in three patients These pathological findings were essentially the same as *in those patients in whom the* excised valve was replaced

Group II—Mitral insufficiency and myocardial revascularization From 1970 to 1977 67 patients were operated upon with myocardial revascularization and mitral repair of replacement In 57 patients mitral insufficiency occurred secondary to coronary artery disease and in 10 the patient s knowledge of *mitral insufficiency antedated the* history of coronary artery disease Repair was feasible in 55 of these patients (82 per cent) Of *these 55 patients undergoing repair,* 19 were women and 36 were men between 42 and 72 years of age (mean 59) Twenty seven patients were in New York Heart Association Class III and 28 were in Class IV The patients were classified on the basis of fatigue dyspnea and congestive heart failure These symptoms were accompanied by angina in 46 patients but severity of angina was not used for classification Eleven patients had Grade II/VI 26 had Grade III/VI and 18 Grade IV/VI mitral insufficiency The amount of insuf*ficiency was determined as follows The cardiac* output was obtained by the Fick Principle The stroke volume of the left ventricle was determined by radiographic means with injection of 76 per cent Renografin into the left ventricle If the amount of blood ejected into the left atrium equaled that ejected into the aorta then this was graded as II/VI If the blood ejected into the left atrium was two times the amount ejected into the aorta this was Grade IV/VI If the amount ejected into the left atrium was three times the amount ejected into the aorta, this was graded as VI/VI

The pulmonary artery pressure was measured *prior to* left ventriculography and coronary arteriography in 27 patients These varied from a normal of 24/13 to a high of 119/61 with 16 patients *(59 per cent) having* a pulmonary artery systolic pressure of 50 mm Hg or more The left ventricular end diastolic pressure prior to radiopaque studies was measured in 35 patients and varied from *7 mm Hg to 38* Twenty nine patients (83 per cent) had an end diastolic pressure of 15 mm Hg (mean 22 6) or greater The ejection fraction was also measured prior to coronary arteriography and ranged from 0 15 to 0 7 in these 55 patients

Thirty three patients had a ruptured or infarcted papillary muscle or torn chordae ten*dineae with secondary annular dilatation* Twenty two patients had a dilated annulus only At operation 92 vein grafts and six left internal mammary arteries were employed for myocardial revascularization

Results

Group I There were 7 hospital deaths (5 per *cent) in the 145 patients with mitral* valve repair Repair failed in 12 patients (8 per cent) from 1 month to 14 years (mean 4 6 years) after the initial operation *Table I Two of these* patients had a second repair 7½ and 8¼ years after the first operation and both are doing well without a murmur 1 and 7 years following the second operation In one of these two patients tricuspid repair as described in 1965[11] was also successfully performed at the time of the second operation Of the 10 patients with subsequent valve replacement seven patients are alive 9 months to 9½ years after mitral valve replacement

There were 30 (20 per cent) late deaths from 3 *months to 10 years (mean 5 years)* after mitral valve repair Table II Two of the 30 late deaths were due to hepatitis 12 were due to myocardial infarction and six deaths were due to carcinoma or leukemia Thromboembolic events occurred in four patients followed for a total of 922 years 0 4 per cent per patient year *These four* emboli resulted in the hospital death in one patient and late death in two patients The fourth patient had a cerebral vascular accident 2¼ years after *mitral* repair from which he recovered completely but died 6½ years later The autopsy revealed a recent myocardial infarct with pulmonary emboli Change in the New York Heart Association classification as judged by a physician is noted in Table III The actuarial curve revealed a survivability of 61 5% (±5 5%) at 17 years (Fig 3) Of the 10 patients with subsequent valve replacement one is lost to follow up and seven patients are

a Hancock porcine valve were free of emboli They furthermore stated that there was a linearized thromboembolism rate of 5 2 per cent per patient year—a very high rate for the Hancock glutaraldehyde porcine valve at first thought to be emboli free

There is a paucity of reports of the results for patients operated upon with mitral replacement with glutaraldehyde treated porcine valves *with concomitant* coronary artery disease or where the mitral insufficiency was secondary to coronary artery disease The reports include very few patients and are as follows Horowitz and coworkers reported one death among 23 patients who had isolated mitral valve replacement with the Hancock glutaraldehyde preserved porcine heterograft without revascularization and two operative deaths among the remaining nine patients who had additional valve surgery or coronary artery grafting

In the report by Buch and associates noted previously they reported on 120 patients undergoing mitral valve replacement with the Hancock stabilized glutaraldehyde process porcine xenograft from March 1971 through April 1975 There was a group of 23 patients who had mitral valve disease with coronary artery disease Twelve of these had rheumatic valvular disease and coronary artery disease and the other 11 had coronary artery disease and nonrheumatic mitral regurgitation Six of these 23 patients (26 per cent) died within the first 30 days following replacement of the patient s mitral valve with a porcine valve Three more patients died after discharge from the hospital so that there were nine deaths in this group of 23 patients with mitral replacement and coronary artery disease Fourteen of these 23 patients had aorto coronary bypass grafts

In the report of Stinson and colleagues quoted previously they reported in 1977 on 243 patients with isolated replacement of the mitral valve with the Hancock glutaraldehyde preserved porcine aortic valve xenografts They stated that Mitral valve patients with associated coronary artery disease accounted for a substantial portion of both early and late deaths For example in 54 patients the diagnosis of coronary artery disease was established by coronary angiography electrocardiographic evidence of previous myocardial infarction or postmortem examination within one year after operation Operative mortality rate in this group was 18 5 per cent and the survival rate of 2 years was only 56 (±7 8) per cent Patients undergoing simultaneous coronary artery bypass grafting for angiographically defined coronary artery lesions fared similarly

In our 55 patients with mitral valve repair for significant mitral insufficiency and myocardial revascularization there were two (4 per cent) operative deaths and six late deaths (11 per cent) The operative and long term results were fairly similar for the patients with an ejection fraction of 0 45 to 0 70 and for the patients with an ejection fraction of 0 25 to 0 40 For the former there were no operative deaths for 27 patients and three late deaths for a total of three deaths (11 per cent) and for the latter one operative death in 24 patients and one late death for a total of two deaths (8 per cent) For patients with an ejection fraction of 0 1 to 0 2 there was one operative death in four patients operated upon however only one long term survival By actuarial methods the 7 year survival for the 55 patients with repair and revascularization including the operative mortality rate of 4 per cent was 80 per cent ± 6 per cent Fig 3 reveals the actuarial curve of our two groups of patients undergoing repair at 17 years for Group I and 7 years for Group II

There was one peripheral thromboembolic episode in the 55 patients with repair followed for a total of 164 years for a 0 6 per cent rate per year There is again a significant difference in the results of the patients with repair and revascularization compared to those series with replacement with a prosthesis or glutaraldehyde porcine valve and revascularization

Although the use of the porcine valve for mitral valve replacement may have reduced the incidence of peripheral embolization compared to other prostheses the number of emboli with this valve is still unacceptably high The uncertain long term durability of porcine valves also continues to be of great concern to most physicians and surgeons If the experience of ours and others with homografts is a logical basis for this concern then the use of glutaraldehyde treated porcine valves as well as other prostheses must be restricted to the minority of patients with mitral insufficiency in whom valve repair is not feasible

We would agree completely with Burch and Giles that the physician should not consider the patient cured once he has undergone cardiac

Table V Mitral insufficiency repair and myocardial revascularization—late deaths

Ejection fraction	Cause of death	Months postop
0 60	Cerebral hemorrhage (on sodium warfarin/prothrombin time 10%)	7
0 18	Cardiac arrest	8
0 46	Pulmonary emboli	3
0 35	Mediastinitis	3
0 68	Unknown	18
0 15	Died in sleep	11

Table VI Mitral repair and myocardial revascularization NYHA functional classification of 47 surviving patients

	To postoperative class			
	IV	III	II	I
Preoperative class IV	–	2	14	5
III	–	1	11	14
II	–	–	–	–
I	–	–	–	–

report however a subsequent article by Shumway revealed a significant incidence of cerebral emboli with the Hancock glutaraldehyde treated porcine valve

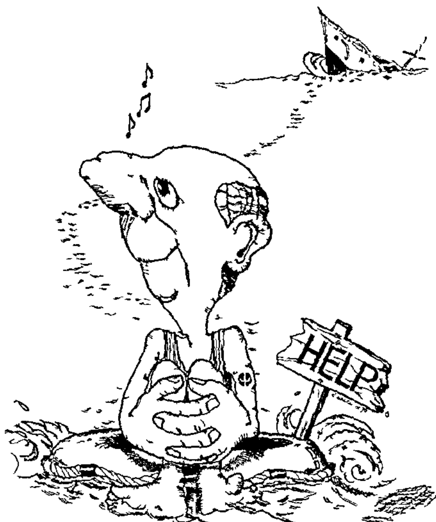
In our 145 patients with pure mitral insufficiency who had a mitral annuloplasty performed from 1959 through 1976, there were seven hospital deaths and 30 late deaths A peripheral embolus occurred in only four of these 145 patients with mitral valve repair followed for a total of 922 years or 0 4 per cent per patient year The over all survival rate calculated by the actuarial method at 17 years is 61 5 per cent (±5 5 per cent) for repair alone This does not include the remaining seven of 10 patients still alive after subsequent valve replacement Of the original 145 patients with repair there are 96 alive with mitral repair and seven more alive after subsequent replacement for a total of 103 living (71 per cent) Of the 30 late deaths two died of hepatitis six died of cancer and 12 patients died of myocardial infarction Approximately ⅔ of the deaths were unrelated to the mitral repair Two patients with repair and one with subsequent replacement are lost to follow up and these are counted as dead There would appear to be a significant difference in results with the group of patients reported by Salomon Stinson Griepp and Shumway with replacement for pure mitral insufficiency Our patient group included 14 patients with a history of angina and infarction, a subset with a poorer prognosis because revascularization was not performed for these patients prior to 1970 Our patient group also included a subset of 68 patients with pure mitral insufficiency with a history of rheumatic fever However, neither at surgery by visualizing the valve or myocardium or in long term longevity could one detect any difference in this subset or the subset with mitral valve prolapse with pure mitral insufficiency without a prior history of rheumatic fever

In 1976 Starr and colleagues[14] reported on 290 patients who had isolated mitral valve replacement for single mitral valve disease with their currently used prostheses These were the non cloth covered Model 6120 prosthesis and the cloth covered composite seat Model 6310 6320 prosthesis inserted between 1965 and 1975 There was a 6 6 per cent combined operative mortality rate There was a 58 per cent observed survival at 10 years for operative survivors only so that the observed survival is closer to 51 per cent at 10 years if one includes the operative mortality rate They stated that for operative survivors, At 6 years the chance to be embolus free is 85 per cent with the cloth covered prosthesis and 66 per cent with the non cloth covered prosthesis The chance to be embolus free at 10 years with the non cloth covered prosthesis is 51 per cent —obviously a high incidence of peripheral embolization compared to repair

Buch and associates[15] reported in 1975 on mitral valve replacement with the Hancock stabilized gluteraldehyde valve The predicted survival of 87 patients without coronary artery disease or prior prosthetic valve replacements was 87 5 per cent at 2 years and 77 5 per cent at 4 years There were four thromboembolic episodes a rate of 2 4 per cent per patient year

In 1977 Stinson and associates[16] reported on the long term experience with the Hancock porcine valve in the mitral area There were 243 patients with isolated replacement of the mitral valve The operative mortality rate was 7 8 per cent Actuarial analysis at 4 4 years revealed a survival rate of 78 per cent At this same interval 92 per cent of the patients with mitral replacement with

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valve replacement, but rather should consider him to be the subject of meticulous long term medical care We would also go one step further to urge the surgeon to do his best to repair the mitral valve before considering replacement with any type of valve presently available

Summary

There has been skepticism since the early days of open heart surgery that good long term or even short term results were possible with repair for pure mitral insufficiency The authors report 145 patients in whom a markedly insufficient mitral valve was repaired 6 months to 17 years previously and another 55 patients in whom repair of the insufficient mitral valve was performed along with myocardial revascularization from 6 months to 7 years previously Comparative data with other published work reveals superior results with repair than with replacement with Starr Edwards and Hancock glutaraldehyde treated porcine valves and with far less emboli Conservatism is urged in operating upon patients with mitral insufficiency Repair of the valve rather than replacement is stressed for those patients requiring surgery

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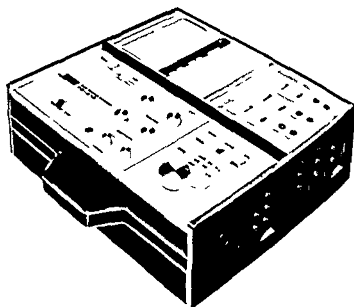
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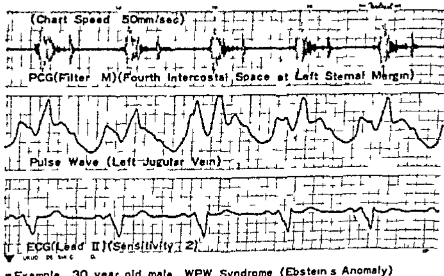
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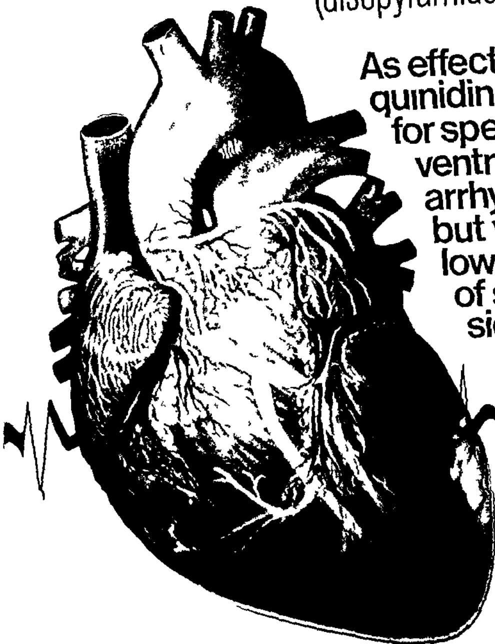
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Excellent patient tolerance—lower incidence of severe side effects than quinidine and significa[illegible] [illegible]er tolerated

Dose related plasma levels—plasma levels correlate closely with dosage

Norpace effect on hemodynamics—*rarely* alters blood pressure significantly at recom mended oral doses and may reduce cardiac output by about 10%

Please *see next page* for a brief summary of prescribing information

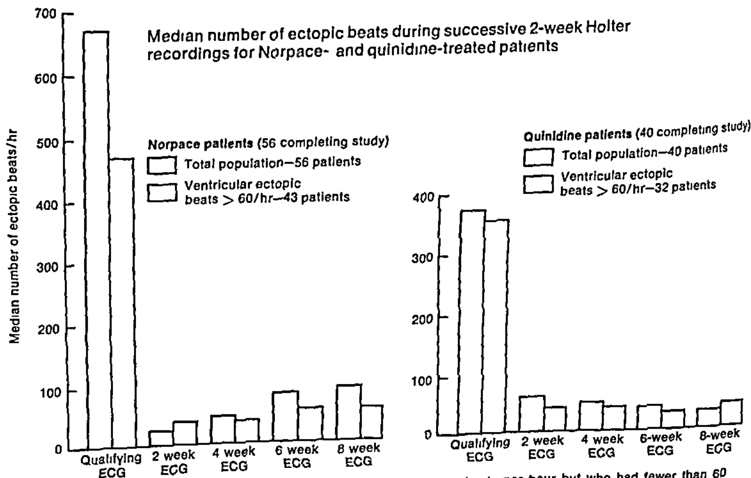
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as effective as quinidine sulfate... with

Results of double-blind controlled studies

A double blind multicenter clinical study involving five investigators was conducted to compare the relative effectiveness and tolerance of Norpace and quinidine sulfate Prior to qualifying for the study each patient had antiarrhythmic medication discontinued for at least one week Nine-hour Holter recordings were then used to establish an admission criterion of at least 60 ectopic beats per hour (PVCs, PACs or combination of the two) All other arrhythmias were excluded except paroxysmal ventricular or atrial tachycardias occurring in conjunction with the above It was apparent that both drugs were capable of reducing ectopic activity and maintaining suppression throughout the course of therapy



Includes patients with more than 60 total (atrial and ventricular) ectopic beats per hour but who had fewer than 60 ventricular ectopic beats per hour

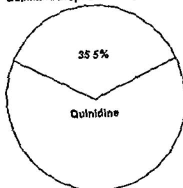
There was no statistically significant difference in reduction of ectopy between the two drugs

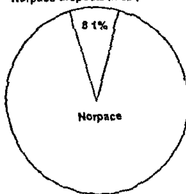
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entıre study population was analyzed
›ıde effects The sıde effects experı
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d and maınly antıcholınergıc ıncludıng
mouth urınary hesıtancy constıpa
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e effects were generally transıent
verse reactıons wıth quınıdıne were
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ns were severe dıarrhea gastroıntes
al symptoms ıncludıng cramps nausea
ıd vomıtıng dızzıness fever and rash





)osage and admınıstratıon

upplıed as 100 mg and 150 mg capsules Dosage should be ındıvıdualızed based on response nd tolerance Usual adult dosage ıs 400 to 800 mg per day gıven ın dıvıded doses four tımes daıly

ııtıal Norpace dosage

Patıents 110 lb and over	150 mg q 6 h
Patıents less than 110 lb	100 mg q 6 h
Patıents wıth specıfıc complıcatıons Patıents wıth possıble cardıac decompensatıon cardıo myopathıes reduced left ventrıcular functıon or hypotensıon due to these or other causes	100 mg q 6 h
Patıents wıth moderate renal ($C_{cr} > 40$ ml/mın) or hepatıc ınsuffıcıency	100 mg q 6 h (200 mg loadıng dose optıonal)
Patıents wıth severe renal ınsuffıcıency ($C_{cr} < 40$ ml/mın)	100 mg gıven approxımately every half lıfe (T½) (200 mg loadıng dose optıonal)
C_{cr} = 40–15 ml/mın	q 10 h
C_{cr} = 15– 5 ml/mın	q 20 h
C_{cr} = 5– 1 ml/mın	q 30 h
In patıents wıthout the complıcatıons specıfıed above ın whom rapıd control of arrhythmıas ıs essentıal therapy may be ınıtıated wıth a loadıng dose of 300 mg (200 mg for patıents under 110 lb)	

For complete Norpace dosage recommendatıons please see full prescrıbıng ınformatıon a y of whıch appears on the next page

SEARLE

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(disopyramide phosphate)



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Indications Norpace is indicated for suppression and prevention of recurrence of the following cardiac arrhythmias when they occur singly or in combination unifocal premature (ectopic) ventricular contractions premature (ectopic) ventricular contractions of multifocal origin paired premature ventricular contractions (couplets) and episodes of ventricular tachycardia (persistent ventricular tachycardia is ordinarily treated with D C cardioversion)

Norpace is equally effective in treating the above arrhythmias in both digitalized and nondigitalized patients It is also equally effective in treating primary cardiac arrhythmias and those which occur in association with organic heart disease including coronary artery disease Oral Norpace has not been adequately studied in patients with acute myocardial infarction or in patients with persistent ventricular tachycardia or atrial arrhythmias and is not indicated for arrhythmias due to digitalis intoxication The value of antiarrhythmic drugs in preventing sudden death in patients with serious ventricular ectopic activity has not been established

Contraindications Cardiogenic shock preexisting second or third degree AV block (if no pacemaker is present) or known hypersensitivity to the drug

Warnings Severe hypotension has been observed primarily in patients with primary cardiomyopathy or inadequately compensated congestive heart failure If hypotension develops Norpace should be discontinued promptly unless hypotension is due to the arrhythmia

Norpace should not be used in the presence of poorly compensated or uncompensated congestive heart failure unless it is exacerbated by or caused by an arrhythmia and proper treatment including optimal digitalization has been accomplished In some patients with marginally compensated heart failure Norpace may worsen cardiac decompensation In these patients progressing congestive heart fa lure should generally be treated with cardiac glycosides and diuretics and the course of treatment closely followed Norpace dosage should be reduced or discontinued if adequate control of congestive failure is not attained

If first-degree heart block develops the dosage of Norpace should be reduced If the block persists continuation of Norpace must depend upon an assessment of the benefit versus the risk Development of second or third degree AV block or uni bi or trifascicular block requires discontinuation of Norpace unless the ventricular rate is adequately controlled by a pacemaker

Because of its anticholinergic properties Norpace should not be used in patients with glaucoma myasthenia gravis or urinary retention unless adequate overriding measures are taken

Precautions If significant widening (greater than 25) of the QRS complex occurs Norpace should be discontinued If Q T prolongation greater than 25 occurs and if ectopy continues monitor closely and consider discontinuing Norpace

Patients with atrial flutter or fibrillation should be digitalized prior to Norpace administration to ensure that drug induced enhancement of AV conduction does not allow a ventricular rate beyond physiologically acceptable limits

The effect of Norpace is presently uncertain in patients with sick sinus syndrome Wolff Parkinson White syndrome or bundle branch block

Patients with myocarditis or other cardiomyopathy may develop significant hypotension in response to the usual dosage of Norpace (disopyramide phosphate)

Norpace should be administered cautiously to patients who are re... ing or who have recently received other antiarrhythmic drugs Exces... widening of the QRS complex and/or prolongation of the Q-T interva... may occur in such instances

Norpace dosage should be reduced in patients with impaired rena... hepatic function and the electrocardiogram carefully monitored for s... of overdosage

Antiarrhythmic drugs may be ineffective in patients with hypoka... Therefore any potassium deficit should be corrected before ins... Norpace therapy

Use in Pregnancy and Lactation Safe use in pregnancy has not bee... established Norpace has been reported to stimulate contractions of t... pregnant uterus The use of Norpace in pregnant women requires tha... the potential benefit be weighed against possible hazards to the fe...

It is not known whether disopyramide is excreted in human milk H... ever studies in rats have shown that the concentration of disopyra... and its metabolites is up to three times greater in milk than in plasma... use of the drug is deemed essential an alternate method of infant fe... should be instituted

Labor and Delivery The effects of Norpace on the fetus during del... or on the course of labor and delivery are unknown

Pediatrics The safety and effectiveness of Norpace in children ha... been established

Adverse Reactions *Anticholinergic* dry mouth urinary hesitancy... stipation blurred vision dry nose/eyes/throat urinary retention *Genitourinary* urinary frequency and urgency *Gastrointestinal* na... pain/bloating/gas anorexia diarrhea vomiting *General* nervousne... dizziness general fatigue/muscle weakness headache malaise *Ca... diovascular* hypotension congestive heart failure cardiac conduct... disturbances edema/weight gain shortness of breath syncope che... pain *Dermatologic* generalized rash/dermatoses The following ha... occurred but a causal relationship is uncertain impotence depress... insomnia hypoglycemia dysuria Acute psychosis and cholestatic ja... dice both reversible have been reported

Dosage and Administration Dosage must be individualized for ea... patient on the basis of response and tolerance The usual adult dos... 400 to 800 mg per day given in divided doses four times daily The r... ommended dosage schedule for most adults is 150 mg every six ho... For patients weighing less than 110 pounds (50 kg) the recommende... dosage is 100 mg every six hours

If rapid control of arrhythmia is essential an initial loading dose of... mg of Norpace (200 mg for patients weighing less than 110 pounds)... recommended For patients with cardiomyopathy or possible cardiac... decompensation a loading dose should not be given and the initial d... limited to 100 mg every six hours with subsequent dosage adjustmen... made gradually under close monitoring

See current complete prescribing information for dosage re... ommendations

How Supplied Capsules containing 100 mg or 150 mg of disopyra... base Available in bottles of 100 capsules

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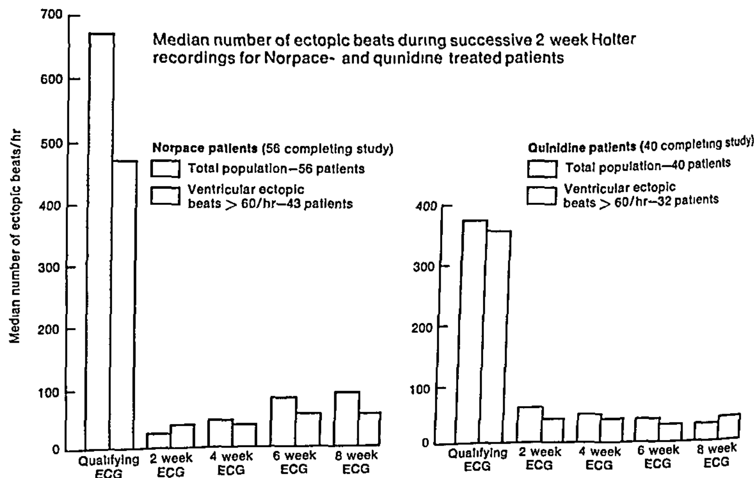
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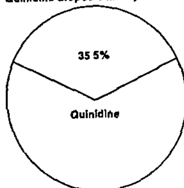
...fective by extensive Holter monitoring

...wer incidence of severe side effects

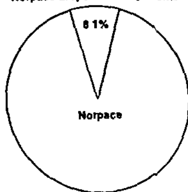
...gnificantly fewer dropouts with Norpace
(disopyramide phosphate)

...entire study population was analyzed ...side effects The side effects experi...ed by Norpace patients were usually ...d and mainly anticholinergic including ... mouth urinary hesitancy constipa...n blurred vision The anticholinergic ...e effects were generally transient ...verse reactions with quinidine were ...re serious and affected a greater num...r of patients The most common symp...ns were severe diarrhea gastrointes...al symptoms including cramps nausea ...d vomiting dizziness fever and rash

Quinidine dropouts in 62 patients



Norpace dropouts in 62 patients



...osage and administration

...upplied as 100-mg and 150-mg capsules Dosage should be individualized based on response ...nd tolerance Usual adult dosage is 400 to 800 mg per day given in divided doses four times daily

...itial Norpace dosage

Patients 110 lb and over	150 mg q 6 h
Patients less than 110 lb	100 mg q 6 h
Patients with specific complications Patients with *possible cardiac decompensation cardiomyopathies reduced left ventricular function* or *hypotension* due to these or other causes	100 mg q 6 h
Patients with moderate renal (C_{cr} > 40 ml/min) or hepatic insufficiency	100 mg q 6 h (200 mg loading dose optional)
Patients with severe renal insufficiency (C_{cr} < 40 ml/min)	100 mg given approximately every half life (T½) (200 mg loading dose optional)
C_{cr} = 40–15 ml/min	q 10 h
C = 15– 5 ml/min	q 20 h
C = 5– 1 ml/min	q 30 h
In patients *without the complications* specified above in whom rapid control of arrhythmias is essential therapy may be initiated with a loading dose of 300 mg (200 mg for patients under 110 lb)	

For complete Norpace dosage recommendations please see full prescribing information a brief summary of which appears on the next page

SEARLE

Norpace®

(disopyramide phosphate)



as effective as quinidine sulfate for specific ventricular arrhythmias...with a lower incidence of severe side effects

Before prescribing Norpace (disopyramide phosphate) please consult current complete prescribing information a summary of which follows

Indications *Norpace is indicated for suppression and prevention of recurrence of the following cardiac arrhythmias when they occur singly or in combination unifocal premature (ectopic) ventricular contractions premature (ectopic) ventricular contractions of multifocal origin paired premature ventricular contractions (couplets)* and episodes of ventricular tachycardia (persistent ventricular tachycardia is ordinarily treated with D C cardioversion)

Norpace is equally effective in treating the above arrhythmias in both digitalized and nondigitalized patients It is also equally effective in treating primary cardiac arrhythmias and those which occur in association with organic heart disease including coronary artery disease Oral Norpace has not been adequately studied in patients with acute myocardial infarction or in patients with persistent ventricular tachycardia or atrial arrhythmias and is not indicated for arrhythmias due to digitalis intoxication The value of antiarrhythmic drugs in preventing sudden death in patients with serious ventricular ectopic activity has not been established

Contraindications Cardiogenic shock preexisting second or third degree AV block (if no pacemaker is present) or known hypersensitivity to the drug

Warnings Severe hypotension has been observed primarily in patients with primary cardiomyopathy or inadequately compensated congestive heart failure If hypotension develops Norpace should be discontinued promptly unless hypotension is due to the arrhythmia

Norpace should not be used in the presence of poorly compensated or uncompensated congestive heart failure unless it is exacerbated by or caused by an arrhythmia and proper treatment including optimal digitalization has been accomplished In some patients with marginally compensated heart failure Norpace may worsen cardiac decompensation In these patients progressing congestive heart failure should generally be treated with cardiac glycosides and diuretics and the course of treatment closely followed Norpace dosage should be reduced or discontinued if adequate control of congestive failure is not attained

If first degree heart block develops the dosage of Norpace should be reduced If the block persists continuation of Norpace must depend upon an assessment of the benefit versus the risk Development of second or third degree AV block or uni bi or trifascicular block requires discontinuation of Norpace unless the ventricular rate is adequately controlled by a pacemaker

Because of its anticholinergic properties Norpace should not be used in patients with glaucoma myasthenia gravis or urinary retention unless adequate overriding measures are taken

Precautions If significant widening (greater than 25) of the QRS complex occurs Norpace should be discontinued If Q T prolongation greater than 25 occurs and if ectopy continues monitor closely and consider discontinuing Norpace

Patients with atrial flutter or fibrillation should be digitalized prior to Norpace administration to ensure that drug induced enhancement of AV conduction does not allow a ventricular rate beyond physiologically acceptable limits

The effect of Norpace is presently uncertain in patients with sick sinus syndrome Wolff Parkinson White syndrome or bundle branch block

Patients with myocarditis or other cardiomyopathy may develop significant hypotension in response to the usual dosage of Norpace (disopyramide phosphate)

Norpace should be administered cautiously to patients who are receiving or who have recently received other antiarrhythmic drugs Excessive widening of the QRS complex and/or prolongation of the Q-T interval may occur in such instances

Norpace dosage should be reduced in patients with impaired renal or hepatic function and the electrocardiogram carefully monitored for signs of overdosage

Antiarrhythmic drugs may be ineffective in patients with hypokalemia Therefore any potassium deficit should be corrected before instituting Norpace therapy

Use in Pregnancy and Lactation Safe use in pregnancy has not been established *Norpace has been reported* to stimulate contractions of the pregnant uterus The use of Norpace in pregnant women requires that the potential benefit be weighed against possible hazards to the fetus

It is not known whether disopyramide is excreted in human milk However *studies in rats have shown that the* concentration of disopyramide and its metabolites is up to three times greater in milk than in plasma If use of the drug is deemed essential an alternate method of infant feeding should be instituted

Labor and Delivery The effects of Norpace on the fetus during delivery or on the course of labor and delivery are unknown

Pediatrics The safety and effectiveness of Norpace in children have not been established

Adverse Reactions *Anticholinergic* dry mouth urinary hesitancy constipation blurred vision dry nose/eyes/throat urinary retention *Genitourinary* urinary frequency and urgency *Gastrointestinal* nausea pain/bloating/gas anorexia diarrhea vomiting *General* nervousness dizziness general fatigue/muscle weakness headache malaise *Cardiovascular* hypotension congestive heart failure cardiac conduction disturbances edema/weight gain shortness of breath syncope chest pain *Dermatologic* generalized rash/dermatoses The following have occurred but a causal relationship is uncertain impotence depression insomnia hypoglycemia dysuria Acute psychosis and cholestatic jaundice both reversible have been reported

Dosage and Administration Dosage must be individualized for each patient on the basis of response and tolerance The usual adult dosage 400 to 800 mg per day given in divided doses four times daily The recommended dosage schedule for most adults is 150 mg every six hours For patients weighing less than 110 pounds (50 kg) the recommended dosage is 100 mg every six hours

If rapid control of arrhythmia is essential an initial loading dose of 300 mg of Norpace (200 mg for patients weighing less than 110 pounds) is recommended For patients with cardiomyopathy or possible cardiac decompensation a loading dose should not be given and the initial dosage limited to 100 mg every six hours with subsequent dosage adjustments made gradually under close monitoring

See current complete prescribing information for dosage recommendations

How Supplied Capsules containing 100 mg or 150 mg of disopyramide base Available in bottles of 100 capsules

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Appraisal and reappraisal of cardiac therapy

Edited by Arthur C DeGraff and Julian Frieden

Infective endocarditis Part II Current therapy

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Many clinical and experimental studies have been undertaken in the past few years to determine optimal therapy for infectious endocarditis which continues to be one of the most serious infectious diseases of man The increased prominence of unusual organisms and the changes in sensitivity patterns of the more characteristic organisms is important therapeutically Therapy often must be started prior to a knowledge of the causative organisms It is useful to review briefly some of the predisposing conditions associated with this disease A knowledge of the probable portal of entry enables one to make an educated guess as to the organisms and therefore the most useful antibiotic or combination of antibiotics

In recent years there has been a decrease in rheumatic heart disease and an increase in the number of people surviving with prosthetic valves congenital heart disease and arteriosclerotic heart disease These people are at an increased risk of bacterial endocarditis so that over all there has been no decrease in the number of patients with bacterial endocarditis

There has also been a change in the types of organisms causing bacterial endocarditis Documentation of bacteremias associated with dental procedures has re affirmed the importance of the mouth flora as a primary source of organisms These organisms usually viridans streptococci have an ability to adhere to heart valves not found in other organisms such as gram negative rods This may be the reason these streptococci remain the leading cause of infective endocarditis The disease is usually sub acute although fulminating infection can occur with these organisms The increased use of intravenous infusions in the hospital and intravenous heroin in the community has increased the incidence of bacteremias which may lead to valvular infections The organisms involved in these latter infections are usually *Staphylococcus aureus* Enterobacteriaceae Sp *Pseudomonas aeruginosa* or enterococci Manipulation or infection of the genitourinary and gastrointestinal tracts may lead to transient bacteremias and valvular infections with Group D streptococci or rarely gram negative rods Group D enterococcus endocarditis rarely seen prior to the introduction of antibiotics[1] is now not uncommon in this setting The disease may be acute or sub acute Group D non enterococcus includes *Streptococcus bovis* increasingly recognized as a cause of endocarditis[2] and *Streptococcus equinus* only rarely a cause of human disease

Staphylococcus aureus is found on normal human skin and may enter the blood stream secondarily to intravenous lines superficial skin infections or wound infections *Staphylococcus aureus* endocarditis may be seen in children including those with hematogenous osteomylitis and this association should be recognized Blood cultures growing *Staphylococcus epidermidis* which is also found on normal skin may represent contamination or infection Continuous bacteremia must be considered to represent intravascular infection and be treated as such although true infection with *Staphylococcus epidermidis* is unusual except in the patients with prosthetic valves

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Received for publication April 6 1978

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0002-8 03/ 8 0296-0263$00 0/0

they may be very sensitive or relatively resistant to penicillin[15] They are treated in the same way as described for viridans streptococci

Staphylococcus aureus

If the organism is known to be sensitive to penicillin, that antibiotic is the drug of choice Few strains of *Staphylococcus aureus* are sensitive, however, and for this reason initial therapy of staphylococcal infections is with a penicillinase resistant penicillin such as *nafcillin or oxacillin* The dose of penicillin is similar to that for sensitive viridans streptococci, the dose of nafcillin is 1 gram intravenously every 2 hours or 2 grams intravenously every four hours Patients occasionally complain of pain when these antibiotics are given intravenously and the infusion may be given more slowly in these situations Recent data, both in vitro and in animals suggest that the combination of nafcillin and gentamicin results in more rapid killing of *Staphylococcus aureus* than nafcillin alone The advantage of rapid killing is that destruction of the valve which may be seen with *Staphylococcus aureus* infections in particular may be prevented Controlled clinical trials are currently underway to test this combination of drugs in large numbers of patients with *Staphylococcus aureus* endocarditis In a small study by Watanakunakorn and Baird[16] there appeared to be little difference between patients treated with the combination and those treated with nafcillin alone For the penicillin allergic patient in whom cephalosporins may be considered, we prefer cephalothin since all cephalosporins may not be equally effective in therapy of staphylococcal infections If the risk of hypersensitivity reactions is considered prohibitive to the use of cephalosporins vancomycin 500 mg intravenously every six hours, or one gram every twelve hours may be used A recently recognized problem with the penicillinase resistant penicillins, cephalosporins and vancomycin is the so called tolerance of certain strains of *Staphylococcus aureus* to these antibiotics In these strains the difference between the MIC and the MBC is thirty two fold or higher This contrasts with the usual two to fourfold differences seen in most strains These tolerant strains are resistant to the action of these drugs although they are reported as sensitive by the Kirby Bauer disc assay which co relates with the MIC only The clinical significance of this phenomenon is not known However, if the patient is not responding well on the usual antibiotic regimen, and the spread in MIC/MBC is demonstrated, several antibiotic combinations such as nafcillin/gentamicin should be tested and the optimal one chosen Intrinsic resistance to methicillin and other penicillinase resistant penicillins which may be recognized by the Kirby Bauer disc assay has not been a major problem in this country, although it may be seen occasionally Disc sensitivities which suggest that an organism is resistant to methicillin and sensitive to cephalosporin are probably inaccurate These latter strains of *Staphylococcus aureus* are resistant usually to cephalosporins also but unlike the tolerant organisms are frequently sensitive to vancomycin At least six weeks of intravenous therapy is most commonly used for *Staphylococcus aureus* endocarditis

There is some uncertainty about duration of therapy for patients who have one or possible two blood cultures positive for *Staphylococcus aureus* secondary to removable foci of infection Commonly a four to six week course has been recommended, but therapy in these cases must be individualized Iannini and Crossley[17] suggest that a ten day course of antistaphylococcal antibiotics is sufficient, but Watanakunakorn and Baird[18] reiterate that in their experience endocarditis is commonly seen in such patients It is essential in these situations that at least three to five blood cultures be obtained over several hours and if these are positive for *Staphylococcus aureus* the patient should be treated as if he or she has endocarditis

Staphylococcus epidermidis

Staphylococcus epidermidis may be sensitive to penicillin or the penicillinase resistant penicillins in which case therapy is similar to that of *Staphylococcus aureus* Some strains of *Staphylococcus epidermidis* are resistant by tube dilution assays to these antibiotics even when disc tests indicate sensitivity to the cephalosporins Recent animal data indicate that a combination of vancomycin and gentamicin may be the most active combination for nafcillin resistant *Staphylococcus epidermidis*[19]

Anaerobic organisms

Anaerobic organisms are rare causes of infective endocarditis The gram positive cocci such as peptostreptococcus and peptococcus are usual

sensitive to penicillin These infections can be treated with high doses of penicillin such as 24 millions units per day Patients who are allergic to penicillin or patients who have *Bacteroides fragilis* (an anaerobic gram negative rod) infections present problems For the allergic patient desensitization and treatment with penicillin may be the therapeutic regimen of choice For the patient with *Bacteroides fragilis* infective endocarditis the choice of drugs is limited as these organisms are commonly resistant to penicillin and sensitive only to drugs considered to be bacteriostatic and not bacteriocidal Clindamycin has been reported to be bacteriocidal for some strains of *Bacteroides fragilis*[1] and if this is demonstrated for a particular organism this drug could be used in doses of 300 mg intravenously every four to six hours Serum bactericidal levels must be monitored and the patient carefully observed for evidence of toxic side effects The most common side effect is diarrhea which can lead to pseudomembranous colitis This serious effect is not common especially if the drug is stopped as soon as diarrhea begins The process may be reversible with cholestyramine[2] Cardiac arrythmias and liver function abnormalities are occasionally observed The only bacteriocidal drug for treating *Bacteroides fragilis* endocarditis at the present time is metronidazole Although this drug has recently been shown to be carcinogenic in mice in this serious situation it may be the best drug Cephoxitin a new cephalosporin may prove to be useful in treating infections with *Bacteroides fragilis* Preliminary data indicates that cephoxitin has activity against these organisms and it is a relatively non toxic drug Currently it is available only for research purposes

Aerobic gram negative rods

Aerobic gram negative rods rarely cause infective endocarditis except in unusual circumstances such as in post valvular replacement infections and in drug addicted persons

Some of these organisms such as *Escherichia coli* and *Proteus mirabilis* may be sensitive to ampicillin and cephalothin other such as *Klebsiella pneumoniae* are resistant to ampicillin but may be sensitive to cephalothin and others such as *Pseudomonas aeruginosa* are resistant to ampicillin and cephalothin but are usually sensitive to gentamicin Some hospitals are now reporting gram negative rods which are resistant to gentamicin and sensitive only to amikacin The least toxic bactericidal drug should be used and therapy should continue for four and possibly six weeks Combination of drugs such as cephalothin and gentamicin may be synergistic against Klebsiella and are suggested in those infections with organisms sensitive to both drugs If the organism is *Pseudomonas aeruginosa* and it is sensitive to both carbenicillin and tobramycin the combination should be used Ticarcillin may be used in place of carbenicillin and gentamicin in place of tobramycin The dose of tobramycin for pseudomonas infections is 1 5 mg /Kg intramuscularly every eight hours and carbenicillin is given in dose of 4 to 6 grams intravenously every four hours Carbenicillin may cause hypokalemic alkalosis and/or a bleeding diathesis the latter especially in patients with impaired renal function

Fungal Endocarditis

Fungal endocarditis is rare and occurs almost exclusively in patients who have prosthetic valves prolonged intravenous infusions or heroin addiction Several reports of candida bacteremia following gastrectomies suggest that the risk of this infection may be increased in these patients Rubinstein and colleagues[22] found that the heroin addicted persons were likely to have unusual species of candida such as parapsilosis and tropicalis while the patients who had had cardiac surgery were infected with candida albicans or aspergillus

It is difficult to differentiate transient fungemia from actual infection Endocarditis has been documented in patients several months after so called transient fungemia[2] Medoff and colleagues[3] suggests a short course of amphotericin for patients with transient fungemia This might apply to those individuals who are at increased risk of fungal infections However since most individuals who develop transient candida fungemia respond to simple maneuvers such as discontinuation of intravenous or bladder catheters we would recommend these procedures for the majority of patients If blood cultures are positive following discontinuation of the catheters antifungal therapy should be instituted In patients with aspergillus endocarditis blood cultures are rarely positive

Once the decision is made that the patient has

they may be very sensitive or relatively resistant to penicillin[15] They are treated in the same way as described for viridans streptococci

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in fact fungal infection, antifungal therapy is instituted Amphotericin intravenously is started, usually at a dose of 1 mg of amphotericin B in 500 ml of 5 per cent dextrose in water The infusion is given over a time period of three to four hours The initial infusion may cause severe reactions such as fever shaking chills, headaches nausea and vomiting and even hypotension Aspirin and benedryl by mouth and hydrocortisone given in doses of 25 to 50 mg in the infusion bottle may be useful if the reactions are poorly tolerated The dose of amphotericin is increased in increments of 5 mg per day to a total dose of 0 5 to 0 6 mg per kilogram of body weight It is usual for the BUN and creatinine to rise Renal function should be closely monitored until these parameters stabilize Bennett ' prefers to keep the BUN below 50 mg per cent and the creatinine below 3 5 mg per cent If these parameters do stabilize the dose may be gradually changed to 1 0 to 1 2 mg per kilogram given every other day Hypokalemia may require potassium therapy The hematocrit may fall secondary to decreased production of erythrocytes The toxic side effects of the drug usually resolve after therapy is discontinued although subtle renal impairment may persist Since fungal endocarditis rarely, if ever responds to medical therapy alone replacement of the infected valve is usually undertaken after a week or 10 days of therapy from the time the optimal dose is achieved Chemotherapy is continued for at least 4 to 6 weeks after surgery

Some species of fungi may be sensitive to five fluorocytosine There is very little data regarding the effectiveness of this drug in endocarditis although the combination with amphotericin B may be additive or minimally synergistic [25] The dose of drug is 30 mg per kilogram by mouth, every six hours in patients with normal renal function Because of the leukopenia and thrombocytopenia associated with this drug and because its use in endocarditis has been minimal we do not recommend it in patients with decreased renal function

Abacteremic endocarditis

For patients in whom the clinical suspicion of endocarditis is very high but blood cultures are negative, penicillin one million units intravenously every two hours and streptomycin 500 mg intramuscularly every 12 hours is a rational regimen This combination treats viridans streptococci, enterococcus, and some of the unusual pathogens mentioned Penicillin alone may result in a clinical response but not a microbiological cure If the patient does not respond to this regimen nafcillin 1 gram every two hours may be added although *Staphylococcus aureus* is such an invasive organism it is unlikely that abacteremic endocarditis is seen in *Staphylococcus aureus* infections, unless the patient has had antibiotics prior to blood culturing

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Hypertension and the cerebral circulation—its relevance to the elderly

Jackson and colleagues described six patients aged between 64 and 81 years in whom antihypertensive therapy had been started and had resulted in marked reductions in blood pressure Associated with the reductions in blood pressure were syncopal episodes They concluded that in the elderly the decrease in elasticity in the cerebral vessels together with the probable presence of atheromatous change in these vessels might lead to a critical reduction in cerebral blood flow when a major reduction in blood pressure occurred In recent years there have been several studies which provide evidence to support this viewpoint

Cerebral blood flow in normotensive animals and in man is maintained constant despite variations in blood pressure in the course of everyday events [2] In other words autoregulation of cerebral blood flow occurs When pressure rises acutely the cerebral vessels constrict and when pressure falls the cerebral vessels dilate The net result is that cerebral blood flow remains unaltered over a fairly wide range of perfusion pressures.

The absolute values for cerebral blood flow are the same in both hypertensive and normotensive people Similar values for cerebral blood flow have also been found in normotensive and hypertensive baboons However the range of pressures over which the hypertensive individual can maintain a constant cerebral perfusion is different in hypertensive subjects when compared to normotensive subjects Almost invariably the whole autoregulatory curve is shifted to higher levels of mean arterial blood pressure in hypertension Furthermore the range of blood pressure over which the hypertensive individual can maintain a constant cerebral blood flow may be somewhat less than in the normotensive person These differences may be explained on structural grounds In hypertensive rats it has been shown that the vessels of the perfused hindquarters are less capable of dilating maximally when compared to vessels from paired normotensive rats. Therefore if the impairment of dilatation is also applicable to the cerebral vessels in hypertension and there does not seem to be any good reason why it should not be it is evident that the pattern of cerebral blood flow autoregulation would be different from that seen in the normotensive cerebral circulation Specifically the diminished ability to dilate would impair the responses of the cerebral vessels when blood pressure is lowered markedly in an acute way Thus the net result would be that cerebral blood flow would start to fall at higher levels of mean arterial blood pressure in hypertensive individuals and therefore there would be evidence of brain hypoperfusion at pressures that might well be regarded as normal and the ideal therapeutic end point

Blood vessels tend to become less distensible as ageing progresses It may therefore follow that elderly people *per se* are less tolerant to major reductions in cerebral perfusion pressure than are those of a younger age group Super added hypertension may compound the issue such that in the elderly hypertensive subject there is even less cerebral circulatory tolerance to lowering the blood pressure Unfortunately there have so far been no detailed studies of the effect of ageing on the pattern of autoregulation of cerebral blood flow nor have younger hypertensive subjects been compared with elderly hypertensive subjects in this regard

Strandgaard and colleagues showed that the lower limit of autoregulation of cerebral blood flow was not equal to the point at which syncopal symptoms occurred Instead they found that further reductions in blood pressure were required before consciousness started to be impaired No such studies have specifically been performed on the elderly although some of the patients studied by Strandgaard and co workers were in the older age group

The neuropathological sequelae of a precipitate reduction in cerebral blood flow consequent upon over vigorous antihypertensive therapy have been described in two patient [6] In both there was ischemic brain damage of cerebral perfusion type

In view of the continuing controversy as to whether or not antihypertensive therapy is even of any benefit in the elderly it would seem that extremely cautious introduction of such therapy should be the approach if any treatment is contemplated at all Certainly it seems unreasonable to impose vigorous therapy with possible side effects and potentially lethal cerebral complications upon patients in whom the benefit has not yet clearly been shown However it has been found [8] that the changes in the pattern of cerebral blood flow autoregulation in hypertension are to some extent reversible with long term therapy and that larger doses of antihypertensive drugs might be tolerated later in the treatment period as a result It is possible that similar benefit may accrue in elderly hypertensive persons and that the initial extreme caution can be replaced at a later date by a somewhat more vigorous therapeutic approach

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Intramural ramification of the left bundle branch

Attention has been focused recently upon location and distribution of the fascicles of the left bundle branch (LBB) in the human heart since these anatomi al details may have an important bearing on pathophysiology of intraventricular conduction It can be useful therefore to briefly illustrate an ur ual variety in morphology of the LBB

The different and largely unpredictable patterns of subdivision of th LBB hitherto described only refer to the sagittal plane indeed the ramifications of the branch are well known to fan and flatten out in thin bands, over the left subendocardial surface of the ventricular septum Occasional anastomoses of individual LBB fibers with the underlying myocardium are too short to be considered as true extensions of the branch on the frontal plane

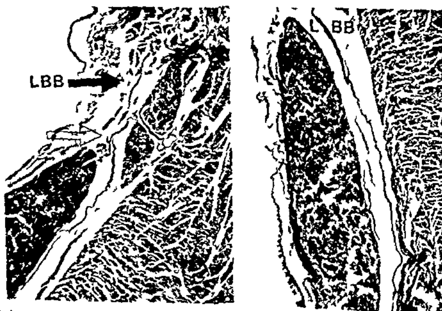


Fig 1 *Left* the root of the LBB *(black arrow)* gives off a medial fascicle *(open arrow)* penetrating the septal myocardium. *Right* further intramural course of the LBB ramification (Azan stain original magnification ×12)

In turn the right bundle branch (RBB) which is a compact fascicle in its middle course normally exhibits a medial bent on the frontal plane entering the myocardial context of the septum (intramural or mimetic tract) Sometimes the entire RBB has been seen to travel inside the septal myocardium

In a 51 year old man who died from heart failure without conduction blocks the conducting system was examined histologically with the technique of longitudinal serial sections and an intramural ramification of the LBB was observed The atrioventricular (AV) node and His bundle were normal at the Hisian bifurcation the root of the LBB was subdivided on the frontal plane into two thin fascicles one lying in the ipsolateral subendocardium while the other penetrated medially the muscle of the upper ventricular septum (Fig 1) This intramural ramification belonged to the posterior part of the LBB and took a straight intraseptal course among thick bundles of working myocardium surrounded by a sheath of loose interstitial tissue (Fig 1) The specific fascicle could be followed downwards and anteriorly over a length of about 1 2 cm along the series of sections and eventually melted with the septal muscle

The present evidence of a distinct proximal intramural division of the LBB in an otherwise normal AV system can be regarded as an apparently unique anatomical variety In a previously described case the intramural root of the LBB belonged to an aberrant Hisian bifurcation completely embedded within the septal myocardium

Besides the morphological interest the intramural location of tracts of the LBB is worthwhile our attention in discussing pathophysiology of LBB conduction disturbances from acute septal infarction particularly

It has been pointed out that a lower oxygen uptake makes the conducting myocells more resistant than the working myocardium to ischemic damage[7] Moreover the LBB owing to its widespread subendocardial layout and closeness to the left ventricle s cavity can be protected from anoxia by transendocardial oxygen diffusion Intramural tracts of the LBB are not likely to share this latter oxygen source with the rest of the branch and thus are comparatively more vulnerable by impaired blood supply through the nutrient arteries

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Of the myocardium and myotonia atrophica (*dystrophica myotonia*)

The striated cardiac muscle and the striated skeletal muscle are known to be different physiologically Although both muscles are striated their differences are further reflected by the differences in their behavior in myotonia congenita and myotonia atrophica For example it is obvious what would happen if the myocardium were to manifest myotonia as skeletal muscle does and the heart were to go into systole and remain contracted for a fairly long period of time as skeletal muscle does Fortunately this state does not develop in heart muscle to any clinically measureable degree If it did the patients would die of systolic arrest It is also interesting that cardiomyopathy and related cardiac disturbances are reported not to exist in association with myotonia congenita but skeletal muscle does develop myotonia It is of further interest that patients with myotonia atrophica have a high incidence of conduction tissue dysfunction[3] with impairment of conduction manifested by various degrees of heart block to complete A V block and complete SA node block Because of this high incidence of pathophysiology of the conduction tissue one wonders if this is not additional evidence that although the disease tends to skip the myocardium itself it strikes the conduction tissue just as it strikes skeletal muscle and therefore cardiac muscle and conduction tissue in the heart are different

The mechanism for the block of the excitation wave front in conduction tissues and within the SA node itself stimulates interesting speculative physiologic considerations For example it is interesting to speculate that the excitation impulse attempts to flow through conduction tissue but a myotonic phenomenon occurs within the cells so that the wave front cannot progress and an additional one cannot even get started This would be myotonia electrica In the case of the SA node the impulse might even be considered to be generated but it is unable to spread through the SA node and escape the node (SA node exit block) to stimulate the atria

Pathologic studies of the myocardium both by light and

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electron microscopy reveal relatively little morphologic change in the myocardium in myotonia atrophica The changes are not specific and may even be the result of previous disease other than the dystrophy itself The histologic and ultrastructural changes in the conduction tissue and myocardium need further investigation as these rare cases become available for study Surely detailed electrophysiologic investigations are needed to learn more about the electric events associated with myotonia atrophica Thoughtful considerations of the cardiac aspects of this disease can be quite provocative

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Mutton s law

When an enterprising reporter asked Willie Sutton the notorious bank robber *why he always robbed banks* he reputedly replied Because that s where the money is Willie s logic spurred Dock to coin the term Sutton s Law as a reminder for physicians to go where the *diagnosis* is

Although many patients benefit from Sutton s Law some profit from a different approach—careful continued observation John Milton gave us a way to remember this when he wrote what I call Milton s Law They also serve who only stand and wait.

Thus Sutton s Law encourages specific well-directed action while Milton s Law pleads for disciplined thoughtful inaction Proper blending of the two is the art of medicine *knowing what to do and when to do it* That s "Mutton s Law

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Steroids in myocardial disease

To the Editor

I read with interest the article by Greenwood Nadas and Fyler (The clinical course of primary myocardial disease in infants and children AMERICAN HEART JOURNAL 92 549 560 1976)

There is one statement made by the authors which I think requires some clarification and explanation The statement concerning the treatment of children with myocardial disease with steroids may be misleading The authors do not state what dose or range of steroids was generally used in these patients. This information is I think of critical importance to the implied statement on the efficacy of steroids

There is as the authors do mention controversy concerning the use of steroids in these conditions Part of this controversy is dose Some experts purport the use of pharmacologic or physiologic doses of steroids (equivalent to 150 mg/kg of hydrocortisone intravenously) for use in cardiovascular emergencies rather than usual doses of parenteral steroids to provide optimal effect with minimal problems.

I don t know whether or not during the times of data collection for this study the use of these physiologic doses of steroids was considered and carried out in these patients This is pertinent information

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Diagnosing magnesium deficiency

To the Editor

With the large number of patients who are now receiving diuretic therapy in clinical practice the incidence of occult magnesium deficiency may indeed be much more common than is generally appreciated The comprehensive review by Burch and Giles brought out very effectively the possible role of magnesium deficiency in the genesis of alcoholic cardiomyopathy ischemic heart disease arrhythmias and electrocardiographic abnormalities We feel that an equally important aspect is the diagnosis of magnesium deficiency and this appears to have received inadequate emphasis in this article

The diagnosis of magnesium deficiency can be difficult. It is clear that serum magnesium levels do not always correlate with total body levels of magnesium[2] Hypomagnesemia is certainly consistent with a magnesium deficient state but a normal serum magnesium level does not rule it out Measurement of urinary magnesium may also be helpful in the diagnosis In addition to serum and urine measurements, Thoren[3] has described a test that utilizes the urinary excretion of magnesium following an intravenous load which may be a more sensitive index of magnesium deficiency In this test 6 mg per kilogram body weight is infused intravenously over a 3 to 4 hour period and the ensuing 24 hour urine collected and analyzed for its magnesium content Accordingly if tissue stores of magnesium are adequate more than 80 per cent of an intravenous dose is excreted within the 24 hour period Experience with this appears to be limited however we feel that to more adequately document a magensium deficient state serum and urine magnesium measurements, a magnesium infusion test and of course the response to magnesium therapy may be more revealing than a single serum magnesium measurement. We appreciate that in many instances these may not be particularly practicable

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Lymphatic drainage of the brain and catarrhea

To the Editor

Földi states that the existence of brain-lymphatic connections has been well established for 100 years however this had already been worked out by the Greeks 2500 years ago

The brain was said to attract moisture from the stomach forming phlegm which then drained out into the eyes nose ears and throat into the cervical glands or down into the lungs and stomach. Lymphostatic encephalopathy was well recognized lethargy and convulsions were attributed to damming up of phlegm in the brain In goats with convulsions Hippocrates noted excess fluid in the subarachnoid spaces significantly although the brains were also infected he placed no importance on this The related condition of benign intracranial hypertension was also known and the dimness of

vision and headache were noted to be relieved by rhinorrhea likewise spontaneous decompression into the mastoid caused otitis media The optic nerves were believed to be the route whereby phlegm drained into the eyes Meningitis and encephalitis would then merely depend on retrograde passage of organisms up pre-existing widely patent lymph pathways As Foldi notes, cherished dogmata—in this case the infectious theory of disease—can completely suppress such simple basic id as As well as explaining cerebral disorders, the concept of catarrhea (the downward defluxion of phlegm) has far more general applicability since phl gm by overloading the drainage vessels can easily cause such disorders as sinusitis otitis media the common cold pneumonia and gastroenteritis depending on its local over accumulation

Foldi mentions perivasal and perineural cranial prelymphatic routes Hippocrates favors a third major route since he specifically remarks that the cranial bones are porous like a sponge and that moisture seeps through these thin bones Such a route neatly explains why hydrocephalus fits optic atrophy facial palsy and deafness are seen in numerous cranial dysostoses like osteopetrosis where osseous occlusion of lymph drainag routes is likely

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Exaggerated impedance waveform—a noninvasive assist

To the Editor

The article by Dr Ramos on the abnormal early diastolic impedance waveform (AM HEART J 94 278 197) describes in excellent fashion the impedance or volume counterpart of a left atrial pressure V wave It is indeed Lababidi s O point (mislabeled in Fig 2) and is synchronous with echo mitral E point.

We have routinely simultaneously combined on the same strip chart recorder echo and impedance traces for almost three years (over 900 cases) and have repeatedly found an exaggerated impedance O (or V) whenever significant mitral regurgitation was present This was true even when the left atrium was greatly enlarged. In our experience an exaggerated O (or V) has proved so reliable that we unhesitatingly diagnose mitral regurgitation in those cases of idiopathic and ischemic congestive cardiomyopathy in which we cannot hear a murmur

Someday we hope the responsible medical profession will undertake a serious investigation of what we are convinced is an excellent practical noninvasive assist

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Reply

To the Editor

It was most exciting to learn that Dr Leschin and his associates have been performing such comprehensive studies. As an author it is most rewarding to become cognizant that in their extensive experience with simultaneous recordings they have accumulated data which tend to support the notion that this abnormal impedance waveform described in my report may represent a functional ventricular inflow impairment

I concur with their hopes for future investigations in this important area "It is only through simultaneous invasive and non invasive studies that the etiology of this abnormal wave form will be clearly elucidated"

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REFERENCE

1 Ramos M U An abnormal early diastolic impedance waveform A predictor of poor prognosis in the cardiac patient? AM HEART J 94 278 1977

Sensing the cardiac electrogram

To the Editor

I would like to thank Drs Furman Hurzeler and De Caprio (Cardiac pacing and pacemakers III Sensing the cardiac electrogram AM HEART J 93 794 1977) for their excellent summary of sensing by cardiac electrodes However I would like to point out a few printing errors

In the discussion on time domain test signals the terms *low frequency cutoff* and *upper cutoff frequency* appear to be interchanged. The slope of a test signal will be a measure of the upper cutoff frequency and the duration will be a measure of low frequency cutoff

Also reference 6 seems to suffer from a printer s devil The first author should be listed as Van Durme et al and the correct numbers are *J Electrocardiol.* 6 97 1973 It would seem however that this reference was meant for some other portion of the paper since it does not provide any reference to *the topic of electrode impedance* I would suggest that the following two references might be more appropriate for the subject of electrode impedance under sensing conditions

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Raber M B Cuddy T E and Israel D A Pacemaker electrodes act as high pass filters on the electrogram (Electrodes as high pass filters) Digest of the Fifth International Symposium on Cardiac Pacing Tokyo March, 1976

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Reply

To the Editor

We appreciate Mr Raber s comments and believe that our differences are substantially semantic It is true that the slope of a test signal will be a measure of the (or should it be its) low frequency cutoff We refer however on page 800 to the cutoff frequencies of the sensing circuit under test not to the test signal Adjustment of the slope to a threshold value causes the upper cutoff frequency of the test signal to coincide with the lower cutoff frequency of the sensing circuit under test and conversely for the adjustment of the duration to a threshold value

We thank Mr Raber for pointing out an error in reference No 6 but in addition reference No 6 in the last line of the left hand column of page 798 should have been listed as No 5 Reference No 5 does discuss electrode impedance We especially appreciate his listing of the two additional excellent references

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REFERENCE

1 Furman S Hurzeler P and De Caprio V Cardiac pacing and pacemakers III Sensing the cardiac electrogram AM HEART J 93 794 1977

Ischemic myocardial disease and alterations in the ECG

To the Editor

The letter regarding subendocardial infarction by Doctors Genovese Salaki Kennedy and Grace in the AMERICAN HEART JOURNAL for October 1976 (92 542 1976) provides helpful information I would like to add further comments which could be helpful in diagnosis and treatment

All aspects of recorded electrocardiograms are the result of chemical changes occurring rhythmically and nearly simultaneously in the living individual cells of the many myocardial cells The myocardium is apparently the only bodily tissue with this rather precise rhythmicity The effect from any other bodily function upon the electrocardiogram has to be mediated through myocardial cell metabolism and will vary with the state of health and chemical reactions within the individual myocardial cells The slow electrical changes known as T waves occurring during the restorative phase of cardiac metabolism usually show changes with lesser metabolic alteration than is needed to change the explosive QRS metabolism Sickened cells have abnormal metabolism and therefore altered electrical output Dead cells have no rhythmic metabolism and therefore do not directly form the electrocardiogram Dead cells may contribute indirectly to the ECG by the catabolic products diffusing to adjacent living cells and acting as foreign substances to alter their metabolism Sickened and dead cells have cell walls altered so that diffusion of enzymes may occur into the pericellular spaces and thence into the general circulation

Alteration of the ECG is dependent upon the degree of metabolic alteration of cells and also upon the mass of cells with altered metabolism A very few cells can be sickened unto death surrounded by a small mass of moderately to slightly sickened cells, and these in turn surrounded by cells with normal or nearly normal metabolism yet little change in even the sensitive T waves will occur because the electrical current reaching the pick up electrode is a summation of all currents reaching the electrode Furthermore cells may sicken to recover or die at varying rates in time This can affect the development of the T wave changes and also affect the appearance of measurably increased enzymes in the blood stream

Our measurements are made of the enzymes in the general circulation at the given moment of drawing blood If a thousand cells die suddenly and are surrounded by a lot of living cells with walls damaged to permit rapid effusion of intracellular enzymes high enzyme measurements can be recorded for many hours If the death of a thousand cells is spread slowly in small increments over a two week period, there may at no time be a rise of enzymes sufficient to furnish what we now consider necessary for diagnosis of myocardial infarction Yet a thousand cells have died in each of the two instances Enzymes have been shown to disappear rapidly from the blood stream so a constant and continued high outpouring is necessary to give high measurements

The above and the following have been illustrated and discussed QS waves do not necessarily occur as a signal of infarction as has been shown in my published and unpublished cases Neither do T waves necessarily have to be inverted to be a signal of infarction An infarction of narrow dimensions zig zagging at an angle may be transmural yet never cause a QS wave in meticulous following over period of 10 20 or 30 years or more as I have followed patients It is true that the use of 12 chest leads instead of the usual six, does give an increased chance of recording QS waves and an increased accuracy of geographic localization of disease Increased value is particularly the case if the electrodes are accurately positioned on the chest wall time after time for year after year and the electrode is held as closely as possible to the chest wall by a rubber strap and the electrode paste is carefully applied to a small area occupied by the chest electrode and the paste is carefully removed from each spot before moving on to the next

Almost all disease can be more easily and better treated if it is recognized in the early stages The Humpty Dumpty method of refusing to recognize as ischemic myocardial disease anything less than a massive transmural infarction has been all too common and pervasive It should have and could have been abandoned long ago

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e O point and diastolic impedance waveform

the Editor

in a recent clinical communcation in the AMERICAN HEART URNAL, Ramos discussed the prognostic value of the stolic waveform of the first derivative of the impedance rdiogram in patients with myocardial insults

Kubicek and associates have developed the electrical impe dance cardiograph referred to as the Minnesota Impedance Cardiograph to assess stroke volume by means of the changes in the transthoracic electrical impedance (Fig 1) which occur during the cardiac cycle In 1971 my associates and I and more recently Naggar and colleagues, demonstrated the strong correlation between the stroke volume measured by the Fick and dye dilution techniques and the stroke volume m asured from the primary waveform of the first derivative of

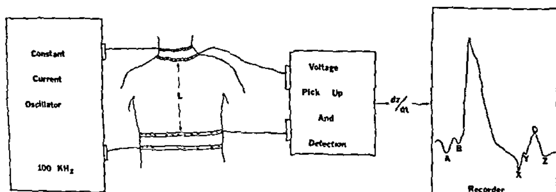


Fig 1 The postion of the electrodes used to record the first derivative thoracic impedance cardiogram

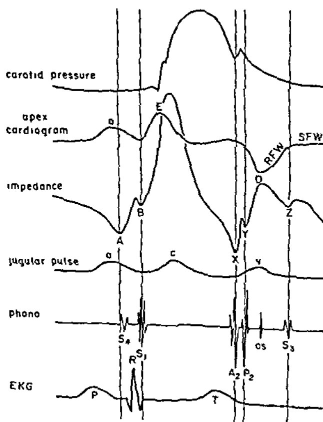


Fig 2 Diagram of the cardiac cycle showing the different waves of the impedance cardiogram as they relate to carotid pressure apex cardiogram jugular impulse phonocardiogram and electrocardiogram

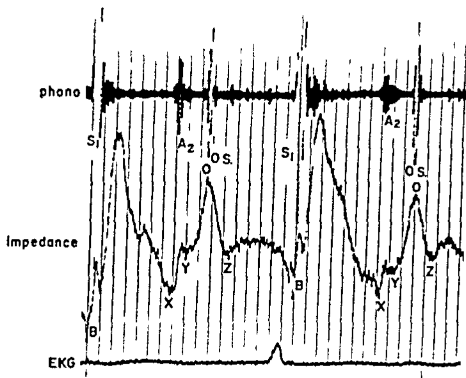


Fig 3 Tracing from a 50 year old man with mitral stenosis Notice the prominent impedance diastolic wave with the O point corresponding to the opening snap

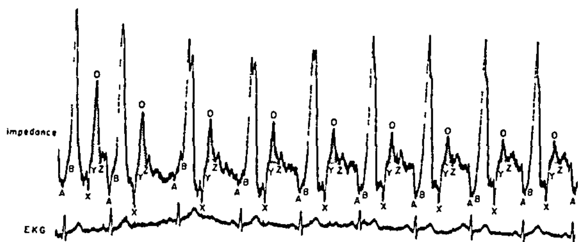


Fig 4 Continuous tracing of impedance cardiogram on a child six years old with held inspiration Notice the very prominent O wave and how it regresses during held inspiration

the impedance cardiogram In 1970 we had also reported a detailed description of the impedance waveform related to the heart sounds and events in the cardiac cycle [3] Dr Ramos mentioned in his article that we had only ten patients with mitral stenosis that showed an O point This may need some clarification in fact the O point was present in *all* patients and normal controls Since our patients were children in whom mitral stenosis is rare we had to borrow those ten patients with mitral stenosis from the adult cardiology service On the other hand I would like to support the observations of Dr Ramos that patients with myocardial disease have a taller diastolic impedance wave and thus higher and more prominent O point

We have observed as shown in Fig 2 that the diastolic wave which starts after the second heart sound has a notch (Z point) corresponding to S and ending with the A point corresponding to the fourth heart sound The peak of this diastolic wave is the O point which correlates well with the O point of the apexcardiogram and the opening snap of patients with mitral stenosis (Fig 3) We have also noticed that the O point of the impedance cardiogram is more prominent in patients with a large left atrium secondary to left ventricular failure mitral stenosis or large left to right shunts It is also more prominent after exercise during high output states and after deep inspiration Fig 4 demonstrates the waveform of the first deviation impedance cardiogram after a deeply held inspiration Notice the very prominent O point and the height of the diastolic wave immediately after the inspiration and

that it becomes less prominent as the inspiration is held for a long time The initial prominence is probably secondary to the initial increase in venous return

In conclusion I believe that the height of the diastolic waveform of the first deviation of the impedance cardiogram is a representative of the left atrial size which is often seen in patients with left ventricular failure and can thus be a prognostic sign as was demonstrated by Dr Ramos

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Reply

To the Editor

I wish to thank Dr Lababidi for his most kind remarks about my article I also wish to thank him for the publication of these figures. Once again these tracings offer a very accurate relationship of the different cardiac events and the way they are reflected in the impedance tracing

His remarks regarding the presence of the O point in all patients and normals are noted Upon reviewing his 1970 article this concept did not become clear since the O point is only mentioned in the 10 patients with mitral stenosis This led me to make the statement which Dr Lababidi feels needs some clarification His remarks are well taken and very much appreciated Despite this the prognostic implication of the abnormal early diastolic impedance waveform I described in my article still applies.

Dr Lababidi s observation of the abnormal waveform in patients with large left atrium mitral stenosis and large left to-right shunts tends to support my theory that this waveform may possibly represent the inability of the ventricles to handle the venous return presented to them during early diastole

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Book reviews

Cardiac Arrhythmias in the Neonate Infant and Child Edited by Nigel K Roberts and Henry Gelband New York 1977 Appleton Century Crofts Inc 533 *pages Price* $32 50

This book edited by Roberts and Gelband is devoted to an *important* and neglected field of cardiology The book is well organized being divided essentially into chapters on embryology of conduction tissues anatomy of the conduction system physiology of the conduction tissues mechanisms of arrhythmias clinical manifestations of arrhythmias and management Disturbances in cardiac mechanism in infants and neonates deserve special consideration and are problems for the pediatric cardiologists and not of adult cardiologists However adult cardiologists were responsible for establishing the fundamental clinical principles of practically all aspects of disturbances in the heart beat in man Their interest had been primarily limited to adults and not the newborn Thus this book provides a good source of information on arrhythmias in early life The need for such a book is evident This reviewer would suggest that all pediatricians and all cardiologists including adult cardiologists own a copy This is a valuable well written and well organized book

Current Cardiovascular Topics vol III Angina Pectoris Edited by Ephraim Donoso M D and Richard Corlin M D New York 1977 Stratton Intercontinental Medical Book Corporation

This issue of *Current Cardiovascular Topics* on angina pectoris consists of an orderly review of angina pectoris as viewed by several selected contributors The book includes discussions of metabolism of ischemic myocardium collateral circulation electrocardiography radiographic studies ventricular function coronary angiography and medical and surgical management The concluding remarks by Gorlin summarize the symposium well The respective subjects are short summaries of many publications reflecting the intensive rate of publications on coronary heart disease The practicing internist and general physician who treat many if not most of the patients with ischemic heart disease will find a great deal of this book difficult to read critically because of their lack of experience with laboratory methods and the special complex methods used in diagnosis and management today Nevertheless this is a good review of most of the present more aggressive approaches to diagnosis and management of ischemic heart disease Ischemic heart disease is one of the most common causes of disease in man

Practical Electrocardiography sixth edition By Henry J L Marriott M D., Baltimore 1977 The Williams & Wilkins Company 333 pages Price $14 50

Marriott s book has been a very popular and useful source for training in electrocardiography He has in the various succeeding editions kept this book up to date The presentations are good and intended for clinicians who have had an interest in cardiology and the interpretation of electrocardiograms for others The emphasis has been on cardiac arrhythmias The approach to teaching the electrocardiographic manifestations of heart disease differs from that of others There is a tendency for the author to teach pattern per se rather than the mechanisms responsible for them This is exemplified for example in the chapter on bundle branch block Again on page 84 the criteria for the diagnosis of left anterior hemiblock would confuse one with the changes due to left ventricular hypertrophy with dilatation Regardless of differences of opinion that might exist among cardiologists concerning aspects of this book it is a good book which would be of greater value to those who already know the fundamental principles of electrocardiography This sixth edition should continue the interest in Marriott s book on practical clinical electrocardiography

Echocardiology *Edited by N Bom The Hague 19*, Martinus *Nijhoff Medical Division 360 pages*

Monographs on echocardiograph (ECHO) have been appearing in rapid succession This new one is an excellent addition to the series The editors have selected a large number of contributors whose discussions are practical reliable and based on fundamental principles of ECHO The papers are grouped into those concerned with clinical echocardiography Doppler instrumentation and application and two dimensional imaging The respective subjects are clearly and thoroughly discussed The illustrations and bibliography are well selected This is a very good book which is highly recommended to all physicians cardiologists and especially to trainees in cardiology

Books received

Clinical Application of Intra aortic Balloon Pump By Hooshang Bolooki, M D Mount Kisco N Y 1977 Futura Publishing Co 500 pages Price $34 50

Rheology of Blood in Diagnostic and Preventive Medicine An Introduction to Clinical Haemorheology By Leopold Dintenfass Ph D London Boston 19 6 Butterworth & Co Ltd 412 pages Price $ 9 00

Computer Electrocardiography Present Status and Criteria By Leon Pordy M D New York 1977 Futura Publishing Co., 374 pages Price $39 50

Diagnostic Electrocardiography second edition By Michael C Ritota M D Philadelphia 1977 J B Lippincott Company 210 pages Price $?2 50

Announcements

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American Heart Journal

September 1978 Volume 96, Number 3

Editorial

Venous thromboembolism after stroke

Charles Warlow M.D. M.R.C.P.
Oxford England

Much is known of the morphological hemodynamic electrical and biochemical changes which occur in the brain after stroke due to either atherothrombotic infarction or intracranial hemorrhage. These changes particularly the development of cerebral edema are largely responsible for death occurring within a few days of stroke and presumably determine the extent of the neurological disabilities of those who survive this early period. Unfortunately therapeutic attempts to reverse or confine these changes have met with little definite success. Later deaths are more often due to non neurological complications which even if not fatal can delay functional recovery and which may be preventable treatable or both. These include pneumonia urinary tract infection peptic ulceration and in particular venous thromboembolism arising in the legs[1]

The clinical signs of deep venous thrombosis (DVT) in the veins of a leg paralyzed as a result of a stroke were described as long ago as 1810 by Ferriar in a patient previously affected by a paralytic stroke" and subsequently in 1833 Lobstein clearly described the pathological appearances Les parois des veines du coté paralytique étaient toutes plus ou moins obstruées par des polypes tandis que celles du cote sain renfermaient un sang dissous et fluide. It is therefore surprising that this complication of stroke is not mentioned in many recent general medical and neurological textbooks. The necropsy frequency of DVT has not been recorded although its occurrence in hemiplegic legs has been commented on[8] Using the [125]I fibrinogen test the frequency during life has been reported in 40 to 53 per cent of patients[1] and the onset is within the first few days after the stroke. The DVT occurs almost exclusively in the paralyzed rather than in the normal leg and this has also been found in 42 chronic hemiplegics where the frequency was 41 per cent and 8 per cent respectively using venography to make the diagnosis[12]

At necropsy Kucera[13] reported the presence of pulmonary embolism in 37 per cent of patients dying from apoplexy and it was the main cause of death in 10 per cent. In another necropsy series embolism was found in only 1 per cent of patients dying within seven days of stroke but in the longer survivors it was present in 25 per cent. The frequency of embolism during life is notoriously difficult to determine and particularly so in stroke patients who may be elderly unconscious or aphasic liable to other cardiopulmonary complications and usually not extensively investigated. In a series in which the necropsy rate was only 21 per cent the over all frequency of pulmonary embolism was 16 per cent but this must have been an underestimate since over half the patients who came to necropsy were shown to have emboli. Therefore approximately half the

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Received for publication Aug. 31 1977

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patients admitted to hospital with an acute stroke resulting in a hemiplegia or hemiparesis will develop a DVT, and up to half of those who die will have pulmonary embolism The excess mortality due to embolism is unknown, but presumably is not negligible and the morbidity due to both embolism and DVT will, of course, delay rehabilitation

Why venous thromboembolism occurs so frequently after stroke is uncertain and whether the mechanism or indeed the frequency depends on whether the stroke is due to atherothrombosis or hemorrhage is unknown Most investigators have not attempted to distinguish between these two main causes of stroke and even those who have may have been mistaken since only with the recent availability of computerized axial tomography has the high frequency of error in their clinical differentiation become glaringly apparent [1] Acute changes in some hemostatic parameters occur after stroke and these include a rise in plasma fibrinogen an increase in fibrinogen/fibrin formation an increase in the platelet count but not adhesion, an increase in circulating platelet aggregates and sensitivity to ADP and adrenaline and a slight shortening of the whole blood clotting time [16 2] There is not unlike many other tissue injury situations, any change in plasminogen activator although those developing DVT tend to have lower levels than those not doing so [2 3] None of these changes can by themselves, account for DVT since they are not confined to individuals developing this complication there are few if any substantial differences in the parameters between those with and without DVT and when DVT does occur it is almost always confined to the paralyzed leg Paralysis, but not its degree must determine the appearance of DVT in susceptible individuals after stroke This susceptibility cannot be defined by changes in any hemostatic or other parameter which has so far been studied and indeed the relationship between such changes and hyper coagulability is very uncertain

The way in which paralysis causes DVT in 'susceptible individuals is not known although there are a number of possibilities Prolonged immobility, whether due to lack of power or sensory loss may perhaps by pressure on the calf cause vein wall trauma and so initiate thrombosis It cannot, however, be mere rest in bed since the non paralyzed leg is normally unaffected by DVT and the duration of bed rest is not related to the frequency of DVT [10] Furthermore there is no very adequate explanation for the occurrence of DVT in the leg and not in the equally immobile arm, perhaps the differing anatomical arrangement of the veins or the larger quantity of vein wall plasminogen activator in the arm play a part here There are presumably local changes in venous blood flow due to impairment of the calf muscle pump but total limb flow is either normal or even increased in hemiplegic legs ' Velocity blood flow may be low compared with the unaffected side [21] ' but when precautions were taken to study patients *before* the development of DVT, no such difference was found In any case venous stasis alone does not cause thrombosis experimentally [5]

There have been no trials of the prevention of venous thromboembolism after stroke One cannot assume that preventive methods shown to be successful in postoperative patients are necessarily useful in stroke or other medical patients when prophylaxis can only be started *after* the stressful event which presumably initiates the DVT Both conventional anticoagulation and low-dose heparin may prevent venous thromboembolism after myocardial infarction [3] but such methods may be dangerous in acute stroke patients due to the difficulty of diagnosing intracranial hemorrhage without computerized axial tomography However with this diagnostic facility to exclude patients with hemorrhage it would be both reasonable and justifiable to mount a trial of anticoagulation after stroke Physical preventive methods, such as calf compression may be helpful if tolerated by the patients but no evidence is available How long prophylaxis should be continued is another unknown factor At the moment although one recognizes the high frequency of venous thromboembolism in stroke patients there is nothing of proven value which will prevent this potentially lethal and commonly troublesome complication

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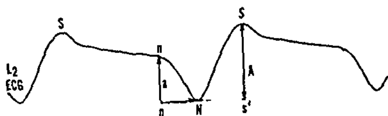


Fig 1 Diagram of a flutter wave as seen in Lead 2 of the electrocardiogram *S s* represents the absolute amplitude *A* (in mm) of a flutter wave (from the highest to the lowest voltage point) *n* is the point where the rate of descent changes producing the left atrial wave The left atrial depolarization is considered to last from n to N Its duration is represented (in msec) by the *n N* interval and its amplitude (in mm) by n N segment *(a)*

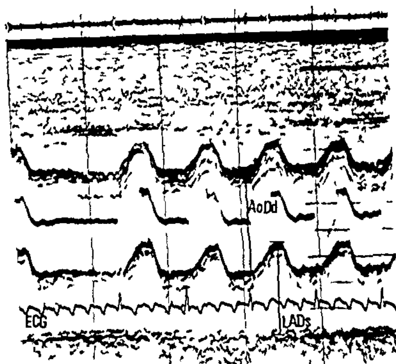


Fig 2 56-year old patient with RHD mitral regurgitation The echocardiogram shows a normal sized left atrium LADs = 3 3 cm LA/AO ratio = 0 92.

matic adjustable beam blanking device which permitted us to record a very clear vector f loop The cut off frequency response was 100 Hz The vectorcardiographic loops were interrupted at a rate of 500 times per second In all tracings the inscription was interrupted by the large end of the time dash

To study the f loop a high degree of magnification is required In our study magnification averaged 3 cm for 1/10 mV To avoid distortion by a preceding T wave a complete f wave cycle occurring just prior to a QRS complex was recorded and analyzed The vectorcardiograms were analyzed for shape sense of direction and speed of inscription (even or uneven)

The echocardiogram was recorded in the supine position with an Ekoline 20 Echograph SKI utilizing a 0 5 inch diameter 2 25 MHz transducer focused at 10 cm with a repetition rate of 1 000 impulses/second The ultrasound transducer was placed in the fourth or fifth left intercostal space close to the sternum The signal from the echograph was displayed and recorded on an Electronics for Medicine VR6 stripchart multichannel oscilloscopic recorder

Ultrasonic scans were recorded from apex to base and echocardiograms were recorded with rigid adherence to the technique and criteria previously established to evaluate left atrial size and the size of the aortic root[7,9] Left atrial

Atrial flutter Electrocardiographic, vectorcardiographic and echocardiographic correlation

Olga Zoneraich M D F A C C
Samuel Zoneraich M D F A C C
Jai J Rhee M D
David Jordan Ph D
Stony Brook and Jamaica N Y

Little is known about the clinical significance of flutter wave contour and amplitude While many studies have analyzed the amplitude of the fibrillatory waves of atrial fibrillation in various types of heart disease the atrial flutter wave eludes the investigators

The renewed interest in the study of atrial flutter results from the data provided by echocardiography in noninvasively assessing atrial size

In a previous report we have proven by ultrasound techniques that there is a direct correlation between mechanical events at the level of the left atrium and electrical activation in atrial flutter

The present prospective study was undertaken to evaluate (1) the amplitude and duration of flutter wave (f) in relation to the size of the left atrium (2) the vectorcardiographic pattern of flutter loops (fsE) in relation to left atrial size and (3) the relation between post conversion sinus P wave (duration shape) f (duration shape) and left atrial dimension

Material and method

The study group was comprised of 32 patients nine females and 23 males They ranged in age from 33 to 94 years with a mean age of 68 years The diagnosis was coronary atherosclerosis (ASHD) in 15 patients (four had associated diabetes mellitus) rheumatic heart disease (RHD) in seven primary cardiomyopathy (PMD) in five patients and miscellaneous (five patients) The electrocardiogram revealed atrial flutter in all (30 of the common type and two of the uncommon type)

Electrocardiograms vectorcardiograms and echocardiograms were recorded during the same morning for each patient

Twelve lead electrocardiograms were recorded and the flutter waves (f) were measured with a magnifying glass by two independent observers

The following parameters were measured and compared between the group with normal left atrium and the group with enlarged left atrium (1) the amplitude (in mm) of left atrial wave (Fig 1) in Lead 2 (n n′ = a) (2) the duration (n N in msec) of the left atrial wave (3) the surface area of the left atrial wave i e the product of a and n N, (4) the maximum amplitude (A) of the f in Lead 2 (S s in mm) and (5) the maximum amplitude of the f ($S\ s_1$) in V_1

Differences between the means were calculated for all measures and tested for significance using t ratios for uncorrelated groups After spontaneous or electrical conversion to sinus rhythm the P wave was analyzed for criteria of left atrial enlargement and intra atrial conduction disturbances The vectorcardiograms were recorded with Hart Electronics PV 5 vectorcardiograph using the Frank lead system Frontal (F) horizontal (H) and right sagittal (S) vectorcardiograms of the f were obtained by using an auto

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Received for publication July 12 1977
Accepted for publication Oct 2 1977

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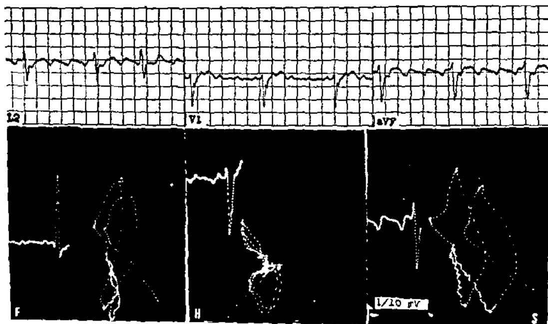


Fig 5 Electrocardiogram and vectorcardiogram of the same patient described in *Fig 4* A = 3 mm n n = 2 mm n N = 80 msec (Large left *atrium and increased n N interval*) The duration of the atrial wave is very well seen in *panel B of Fig 6* The VCG shows pattern I

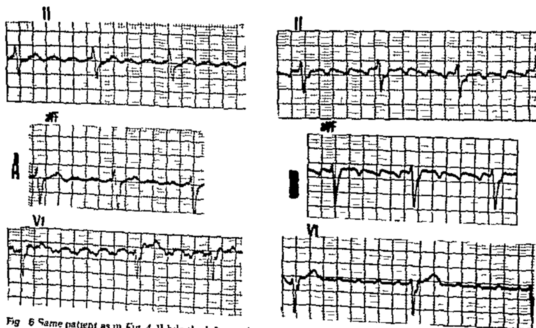


Fig 6 Same patient as in *Fig 4* While the left atrial size remained unchanged the flutter wave contour changed considerably (for details see text)

atrium (NLA) in Group 1 and 18 patients with an enlarged left atrium (ELA) in Group 2

Results

The duration of the left atrial wave in L (n N) varied between 40 and 60 msec in Group 1 with NLA and between 40 to 120 msec in Group 2 with ELA (Figs 3 4 and 5) Seventy five per cent of patients with ELA have a duration of more than 40 msec of n N interval In the group with NLA only four patient (28 per cent) have a duration of the n N interval above 40 msec The amplitude of

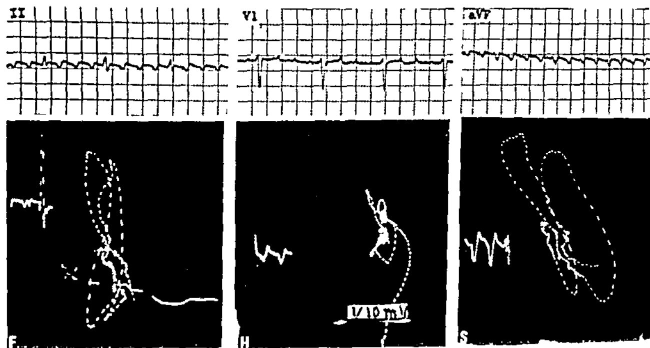


Fig 3 Electrocardiogram and vectorcardiogram (VCG) of the same patient described in *Fig 2* The A in Lead 2 is 2 mm and 1 5 mm in Lead V The n N interval is 50 msec and the amplitude of the left atrial wave is 1 mm (normal size left atrium and short n N) The VCG shows pattern I (a)

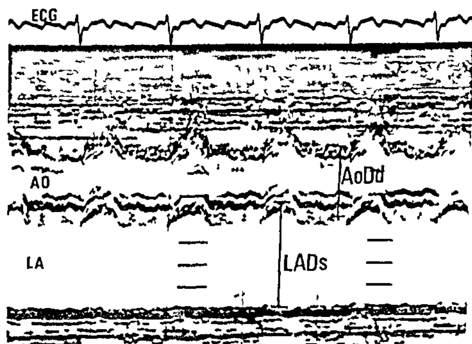


Fig 4 53 year old male patient with ASHD The echocardiogram shows an enlarged left atrium LADs = 4 7 cm LA/AO ratio = 1 52

measurements were taken at the maximum upward motion of the aortic wall which represents end systole (from the anterior edge of the posterior aorta to the interior edge of the posterior left atrial wall)

The left atrium-aortic root ratio was also used to standardize the left atrial dimension This ratio is obtained by dividing the end systolic left atrial dimension by the end diastolic aortic dimension as measured from the outer edge of the anterior aortic wall echo to the inner edge of the posterior wall echo (Fig 2)

The echocardiographic diagnosis of left atrial enlargement was based on (1) transverse left atrial diameter greater than 4 0 cm and (2) ratio of transverse left atrial to aortic root dimension greater than 1 17 Using these criteria 14 patients were classified as having a normal sized left

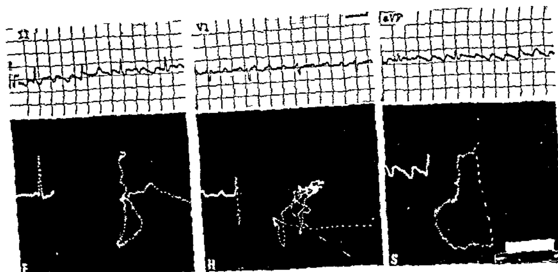


Fig. 8. 60-year-old patient with mitral regurgitation. Left atrium was enlarged. LADs = 4.7 cm. The duration of the left atrial wave is 60 msec. The VCG shows a distorted triangular pattern in *F* and *S* planes with dense conduction delay pattern II (a).

P wave abnormalities. After conversion to sinus rhythm 10 patients (62 per cent) in the group with ELA presented a P wave with a duration of 0.12 sec. or more (two patients from this group failed to convert to regular sinus rhythm). In the group with NLA six patients (43 per cent) had a P wave with a duration of 0.12 sec or more (Table II). The P wave had an enlarged duration and bifid contour in 10 patients (six in Group 1 and four in Group 2).

It is worthwhile to mention that in the group with ELA eight patients who had an abnormal duration of P wave had also an n-N interval of 60 msec. or more while in Group 1 only three had an abnormal duration of P wave and prolonged n-N interval.

Discussion

The clinical classification of flutter based on the form of the f in Leads 2, 3, aV$_F$ and aV$_R$ of the electrocardiogram recognizes two types of flutter: the common and the uncommon type.

In the common type the atrial f waves are inverted in Leads 2 and 3 and aV$_F$ and are upright in aV$_R$ (Fig. 3) and in the uncommon type the f waves are upright in Leads 2 and 3 and aV$_F$ and aV and inverted in Lead aV$_R$.

Neither the theory of focal impulse formation nor that of circus movement can explain all observations in humans or animals.

In the common type the depolarization of the left atrium is considered to proceed in a caudo-cranial direction.

Table II. Duration and contour of sinus P wave as related to left atrial size

Enlarged left atrium (16 patients)				*Normal size left atrium (14 patients)*			
P ≥ 0.12 sec		P < 0.12 sec		P ≥ 0.12 sec		P < 0.12 sec	
10 patients		6 patients		6 patients		8 patients	
Bifid	Dome	Bifid	Normal	Bifid	Dome	Bifid	Normal
6	4	3	3	4	2	1	7

The depolarization process first involves the interatrial septum and reaches the inferolateral wall about the same time as the roof of the left atrium. In the uncommon type the impulse is considered to originate high in the right atrium and the activation of the right atrium precedes that of the left. Alderman and colleagues showed by echocardiographic recordings in three cases of common atrial flutter that the onset of forward motion of the mitral valve coincided with notch to nadir interval in Lead 2 of the electrocardiogram. This suggests that left atrial activation occurs at this time producing the left atrial wave (n-N in Fig. 1). We showed the duration of this wave is influenced by atrial size and/or atrial conduction disturbances.

The amplitude of fibrillatory waves in atrial fibrillation has been studied but no attempt has been made to correlate the amplitude, contour and conduction disturbances of the flutter wave with the size of the left atrium.

Our study demonstrated a good relationship

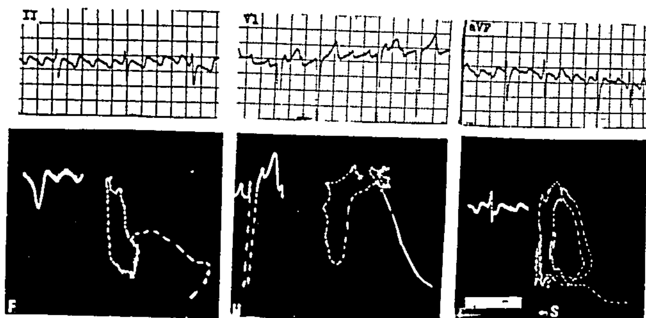


Fig 7 56 year old patient with aortic stenosis Left artial size was normal The artial wave has a duration of 40 msec and the amplitude (A) in Lead 2 is 3 mm The VCG (pattern 1b) shows dense conduction delay

Table I Difference between the means of groups with normal and enlarged left atrium for selected electrocardiographic measures

Variable	Normal $\bar{X}$ (SD)	Enlarged $\bar{X}$ (SD)	t	p
n n (a) in mm	1 19 (42)	1 26 (47)	41	NS
n N duration (in msec)	43 85 (63)	72 91 (3 1)	37 90	< 01
Area (a X n N)	53 7 (24 4)	89 2 (45 9)	2 72	< 01
S s (A) in L (in mm)	2 15 (72)	2 06 (73)	34	NS
S s (A) in V (in mm)	1 51 (56)	1 81 (1 05)	1 11	NS

The value is expressed in arbitrary units (mm msec)

left atrial wave (a) in L varied between 0 5 to 2 2 mm in the group with ELA and between 0 5 and 3 mm in the group with NLA The amplitude of f in L (A) was between 1 and 2 8 mm in the group with ELA and between 1 mm and 3 5 mm in the group with NLA In V_1 the A varied between 1 and 3 mm in the ELA group and between 1 and 2 5 mm in the NLA group The surface area for the group with NLA varied between 40 to 100 arbitrary units and in the group with ELA it varied between 30 and 156 units (mm × msec)

The results of the comparison of the mean differences between the two groups for the five electrocardiographic measures are presented in Table I The means of the group with ELA were significantly greater for the duration of the left atrial wave (t = 37 9 p < 01) and the area under the curve (t = 2 72 p < 01) In other words those individuals with ELA as determined by echocardiography had a significantly longer depolarization time of the left atrium as seen in the electrocardiograms

No significant difference were found for the A of the f as measured by S s_t segment between the two groups in Leads 2 and V_1

Atrial rate in relation of left atrial size In the group with NLA the mean rate was 284 and in group with ELA the mean atrial rate of f was 264

The vectorcardiogram Two vectorcardiographic patterns were present in both groups

1 Pattern I with an elongated elliptical continuously recorded fsE loop in F and S planes (Fig 3) This pattern was subdivided into two subgroups a and b *a* having smooth conductive delays mostly in the left side of the loop (Fig 3) and *b* having scattered patches of conduction delays throughout the entire fsE loop (Figs 4 5 6 and 7)

2 Pattern II exhibited a distorted irregular fsE loop contour This pattern also presented features which allowed us to subdivide it into two subgroups *a* those with triangular shaped f loops in F and S planes with dense conduction delay (Fig 8) *b* Those with very distorted fsE loops with scattered conduction delays (Fig 9) The sense of direction was predominantly counter clockwise (CCW) in the frontal plane CCW or figure of eight in the horizontal plane and clockwise (CW) in the right sagittal plane in both groups In the group with ELA two VCGs had a CW direction in the frontal plane

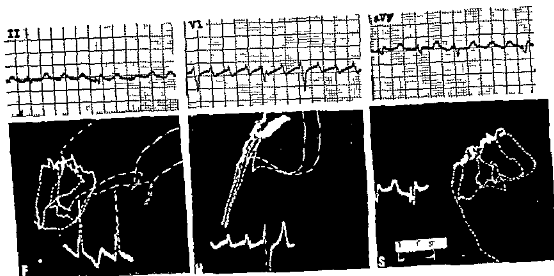


Fig 11 60 year old patient with PMD Left atrium was enlarged (LADs 5 3 cm) The ECG shows the uncommon type flutter with rounded upright f wave in Lead 2 and aV The VCG shows a triangular distorted contour in frontal and sagittal planes and in the horizontal plane a very narrow f loop is oriented anteriorly and to the right

flutter contour Fig 5 shows important changes in the contour and direction of the f wave while the size of the left atrium remains unchanged Such changes may be due to a shift in the origin of the ectopic focus or to conduction disturbances [9]

The vectorcardiographic study of the f wave has been neglected mostly due to difficulties in recording and interpretation Although the continuous f wave makes it difficult to decide the location of the zero point Sano and associates entertained the possibility of identifying the beginning of fsE loop in two patients

Alderman and colleagues[17] reported three patients studied by computer processed vector cardiograph who showed a typical type of flutter activity The vector loops of left atrial depolarization in all three patients were oriented superiorly (corresponding to the notch to nadir interval of Lead 2) This preliminary observation seems to be useful in evaluation of the vectorial atrial forces in common flutter *It is extremely* difficult to determine in the vectorcardiogram the zero point (origin) of the fsE loop The fsE loop recorded by our system offers a distinct advantage One can easily determine the distortions and the conduction delays of the fsE loop Such changes when present might reflect underlying morphological myocardial changes and/or *conduction* disturbances in both atria Our study based on the fsE pattern obtained in 30 patients with flutter of the common type revealed two patterns of atrial depolarization Type I pattern was found most *frequently* (63 per cent in patients with NLA while Type II with distorted pattern and dense conduction delays was seen in 67 per cent of *patients with* ELA The conduction delays and the even speed of depolarization and repolarization seen in many fsE loops could be due to structural changes (fibrotic processes etc) or to *blockage* in the specific pathways[18] of the newly discovered bridges in the atria After conversion of flutter to RSR the PsE loop also shows the presence of intra atrial conduction delays (Fig 10)

In a previous paper we presented evidence that the duration of the P wave is not related to the left atrial size alone Other factors possibly intra atrial conduction disturbances in the specific pathways play an important role in the prolongation of the duration of the P wave and distort the PsE loop

Sixty two per cent of the patients with ELA showed (post conversion) an abnormal sinus P wave and 43 per cent of the patients with NLA who developed flutter showed an abnormal P wave (duration and contour) The bifid type of P wave was predominant in both groups In patients with NLA the abnormal P wave was probably due to conduction disturbances

In two cases we recorded the uncommon type of flutter with upright rounded f in Leads 2 and 3 and aV_F (Fig 11) The VCG showed a distorted

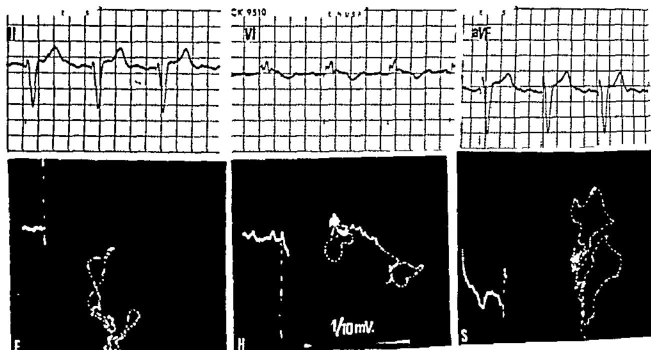


Fig 9 65 year old patient with ASHD Left atrium was enlarged (LADs = 4 2 cm) The flutter waves are very small The VCG shows a very distorted fsE loop with dense conduction delays (pattern IIb)

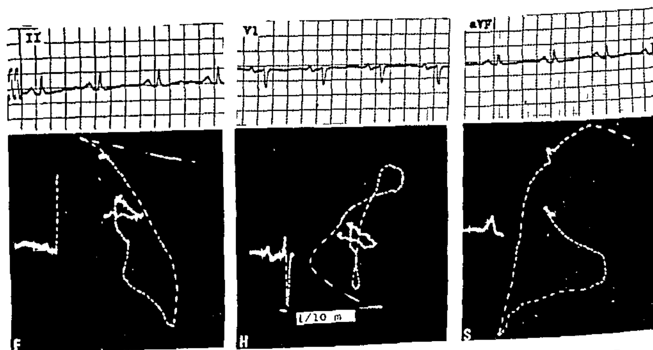


Fig 10 ECG and VCG of the patient described in *Fig 8* recorded after conversion to sinus rhythm The P wave has a duration of 0 14 msec and the PsE shows dense conduction delays (intra atrial conduction disturbances)

between the duration of left atrial depolarization as seen in the f of the electrocardiogram in Lead 2 and the size of the left atrium calculated echocardiographically In 75 per cent of the patients with ELA, the duration of n N interval (left atrial wave) was more than 40 msec while four patients (28 per cent) in the group with NLA had n N duration above 40 msec ($p < 0\ 01$) The surface area of left atrial wave (a × n n) was smaller in patients with NLA (mean 53 7 ± 24 4) as compared to the group of patients with ELA (89 2 ± 45 9 $p < 0\ 01$) (Table I) The A of the f wave in Leads 2 and V_1 of the ECG failed to correlate with the size of the left atrium

In atrial flutter the pathway of atrial depolarization is not fully elucidated [10] Structural and functional changes in the atrial myocardium and of the specific pathways[1] probably change the

Hemorrhagic myocardial infarction associated with aortocoronary bypass revascularization

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A decade of experience with aortocoronary bypass surgery has accumulated since its clinical application initially for the relief of angina pectoris in patients with obstructive coronary artery disease Bringing blood to the blighted ischemic heart muscle is a therapeutic approach of such appealing logic that beginning in 1970 there have been a growing number of reports on the use of aortocoronary bypass for patients with impending or evolving myocardial infarction[2] It was reasoned that aortocoronary bypass performed during the early phase of myocardial infarction might salvage the jeopardized myocardium and reduce the ultimate size of the infarct [2]

Since 1974 the enthusiasm for aortocoronary bypass as an emergency procedure has been dampened by reports from several independent workers of deleterious effects of myocardial reperfusion In closed chest experiments in dogs described by Lang and associates Bre nahan and co workers and Mathur and associates reperfusion after 3 to 5 hours of coronary artery occlusion not only failed to reduce the size of the infarct but had in fact extended the area of myocardial necrosis in 44 to 70 per cent of the animals and the infarction was characteristically hemorrhagic

Our autopsy study of patients with myocardial infarction immediately preceding or following aortocoronary bypass confirms the hazard of hemorrhagic infarction in myocardial revascularization and suggests that this complication may account for the high mortality of evolving and perioperative myocardial infarctions within the first 14 days of aortocoronary bypass as reported by Dawson and associates[16] and by Pifarre and co workers

Material and methods

Between 1968 and 1975 aortocoronary bypass with autogenous saphenous vein grafts was performed on 1 837 patients by an operative technique reported previously The over all graft patency was 84 per cent in 281 patients with 492 vein grafts at a mean follow up of 19 months (range 0 to 75 months) Only those patients who died with histologically documented acute myocardial infarction and were autopsied in one of the affiliated hospitals a total of 44 patients were included in the present study

The method of postmortem examination of the heart has been described in detail elsewhere The infarcts were dated according to the histologic criteria of Mallory and associates[2] Special attention was directed to the identification of myofibrillar degeneration eosinophilia and wavy distortion of fibers all of these being sensitive markers of acute myocardial ischemia Evidence of adequate healing of infarcts was determined by the identification of (1) in the second week

From th Departm nts of P thol gy Surgery and Med cin Baylor College of Med cin Ho t n T x

Supported in part b Gr nt HL-1 ?4 ?f m th N t al H rt Lung and Blood Inst tu N t nal Inst t tes f Health United States Public H lth Service

Received for public tion July ?6 19??

A epted f r pul lication A g 25 19 7

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0002 -8 03/ 8/0396-0?9 $00 50 0 © 19 8 The C V Mosb Co

contour in frontal and right sagittal planes with dense even conduction delay As long as the electrocardiographic recordings are obtained by conventional leads, it is natural to doubt if this rounded pattern is due to severe conduction disturbances at the atrial level or to a different origin of the ectopic mechanism [21]

Summary

The duration contour and amplitude of atrial flutter wave (f) was studied by electrocardiogram (ECG) and vectorcardiogram (VCG) in 32 patients and was related to the size of the left atrium (LA) measured by the echocardiogram (E) The following ECG parameters were analyzed (1) the duration of left atrial depolarization i e , LA wave (2) the amplitude of LA wave (3) the surface area of LA wave (4) maximum amplitude (A) of f in Leads 2 and V_1 There was good correlation between LA size and the duration of depolarization and surface area ($p < 0.01$) but the maximum amplitude of the f wave in Leads 2 and V_1 failed to predict LA size

The post conversion sinus P wave showed abnormal LA depolarization time ($P > 0.12$ sec) in 62 per cent of patients with enlarged left atrium (ELA) and in 43 per cent of patients with normal size LA (NLA)

The VCG of the flutter wave revealed two patterns (1) an eliptical smooth fsE loop in 63 per cent of patients with NLA and (2) distorted fsE loop in 67 per cent of patients with ELA

Both VCG patterns were subdivided in two subgroups according to the number and location of conduction delays The VCG of post conversion P wave confirmed conduction delays in both groups

We conclude that both the size of the left atrium and conduction delays play a basic role in the duration and contour of left atrial wave

The authors wish to thank Mrs Ada Kamara for her technical assistance and to acknowledge the secretarial assistance of Mrs Karen Franklin

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Table I Preoperative and operative variables in 44 patients with myocardial infarction (MI) associated with aortocoronary bypass (ACB) surgery

Variables	*Group I (14 patients)*	*Group II (13 patients)*	*Group III (17 patients)*
Mean age (yr)	54.2	51.2	57.3
Sex	12M 2F	11M 2F	13M 4F
Hypertension (no of patients)	2	2	2
Left ventricular hypertrophy (no of patients)	8	7	9
Autopsy-confirmed old MI (no of patients)	6	6	9
Mean ACB pump time (h)	2.2	2.0	2.4
Mean number of ACB grafts	2.4	2.5	2.3

Two or more recordings of systolic pressure greater than 140 mm Hg and diastolic pressure greater than 90 mm Hg

Table II Distribution and number of coronary arteries with significant occlusive disease in 44 patients with myocardial infarction associated with aortocoronary bypass surgery

Significant occlusive disease of major coronary arteries	*Number of patients*		
	Group I (14 patients)	*Group II (13 patients)*	*Group III (17 patients)*
Distribution			
Left main coronary artery	1	0	1
Left anterior descending artery	11	11	13
Left circumflex artery	8	7	12
Right coronary artery	9	7	10
Number of vessels involved			
One	0	0	0
Two	4	5	4
Three	9	6	11
Four	1	2	2

Vessels with luminal narrowing of 75 per cent or more

myocardial infarction after aortocoronary bypass as determined by symptoms new Q waves and serum enzyme changes

Hemorrhagic infarcts were evident in 57 per cent of patients (eight of 14) in Group I and 38 per cent (five of 13) in Group II whereas only 6 per cent of patients (one of 17) in Group III had hemorrhagic infarcts (Fig 2) The differences were significant between Groups I and III ($P < 0.005$) and between Groups II and III ($P < 0.05$) but not between Groups I and II In all cases a vein graft had been inserted to the artery supplying the area of infarction and it remained patent Poor runoff due to atherosclerosis of the distal coronary arteries as determined at autopsy was the presumed anatomic basis of myocardial infarction in patients of Groups II and III

In Group I patients with hemorrhagic infarcts there was no discernible difference in amount of hemorrhage between those having a 1 day old infarct and those having a 1 week old infarct On the other hand hemorrhagic infarcts when present were more severe in patients in Group I than in those in Group II

There were no significant differences among the three groups of patients in regard to the following variables mean age sex ratio clinical evidence of hypertension left ventricular hypertrophy autopsy confirmed old myocardial infarcts aortocoronary bypass pump time and the number of aortocoronary bypass grafts (Table I) The distribution and the number of coronary arteries with significant occlusive disease also were similar (Table II) The number of patients with two-vessel or three vessel disease was slightly higher proportionately in Group I (13 of 14 or 93 per cent) than in Group II (11 of 13 or 85 per cent) or Group III (15 of 17 or 88 per cent) but the differences were not significant None



Fig 1 *Left* Heart cut sagittally to show hemorrhagic myocardial infarct of posterior wall of left ventricle *(dark blotchy area)* *Right* Low power magnification photomicrograph of hemorrhagic myocardial infarct infarct is in upper left corner of picture Note that interstitial hemorrhage *(dark linear streaks)* extends well beyond infarct (Hematoxylin and eosin original magnification ×40)

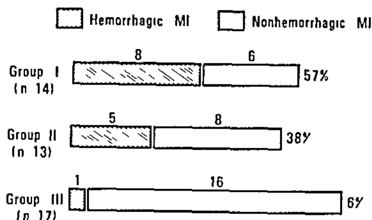


Fig 2 Percentage of hemorrhagic myocardial infarcts *(MI)* in each group of patients who underwent aortocoronary bypass Group I had infarction predating aortocoronary bypass by 1 to 7 days Group II had infarction 1 to 14 days after aortocoronary bypass and group III had infarction 15 to 90 days postoperatively

karyorrhexis of polymorphonuclear leukocytes and ingrowth of blood vessels and fibroblasts (2) in the third week removal of the necrotic muscle by phagocytic leukocytes and influx of lympho cytes and plasma cells, and (3) in the fourth and subsequent weeks condensation of collagen and hyalinization of the fibrous scar tissue

Hemorrhagic myocardial infarct was defined as an infarct with grossly discernible interstitial hemorrhage or microscopically evident extension of the hemorrhage beyond the infarcted zone (Fig 1) The size of the infarct was determined morphologically by the method of Hackel and Ratliff The results were evaluated statistically by means of Fisher's exact method for 2 × 2 tables

Results

Although the indication for aortocoronary bypass was angina pectoris 14 patients (Group I) of the total of 44 had unsuspected evolving myocardial infarction histologically either pre dating aortocoronary bypass from 1 to 7 days or occurring within 12 hours after the operation None of these 14 patients had diagnostic electro cardiographic or serum enzymatic evidence of acute myocardial infarction Thirteen other patients (Group II) were found histologically to have experienced myocardial infarction between the first and fourteenth postoperative days The remaining 17 patients (Group III) had myocardial infarction in the more remote postoperative period of 2 weeks to 3 months after aortocoronary bypass All patients in Groups II and III died with acute myocardial infarction defined as ischemic necrosis of the myocardium 1 day to 4 weeks old The histologic age ' of the infarct corresponded closely to the clinical onset of



Fig. 5. *Upper*, Photomicrograph of border zone of a hemorrhagic myocardial infarct shows focal ischemic necrosis surrounded by interstitial edema and hemorrhage. Necrotic fibers appear darker (more eosinophilic) and show contraction bands in midst of some normal looking fibers. Note that infiltration by polymorphonuclear cells has begun. (Hematoxylin and eosin, original magnification ×240.) *Lower*, High power magnification photomicrograph showing individual cell necrosis (myofibrillar degeneration with contraction bands) surrounded by numerous extravasated red blood cells. (Hematoxylin and eosin, original magnification ×1,200.)

of the second week. In contrast, islands of necrotic muscle in hemorrhagic infarcts appeared to lie dormant in a sea of red blood cells even as late as the fourth week (Fig. 4). Another unfavorable histologic feature of hemorrhagic infarcts was the extension of ischemic injury. Patchy foci of myocardial necrosis often appeared outside the infarcted areas but well within the zone of edema and hemorrhage. The necrosis was characterized by eosinophilia and waviness and myofibrillar degeneration of individual fibers with or without infiltration by polymorphonuclear leukocytes (Fig. 5).

Pathologically, hemorrhagic infarcts also differed from nonhemorrhagic infarcts in regard to infarct size expressed as the percentage of left ventricle involved. The infarct was 50 *per cent* or larger in nine of 14 patients (64 per cent) with

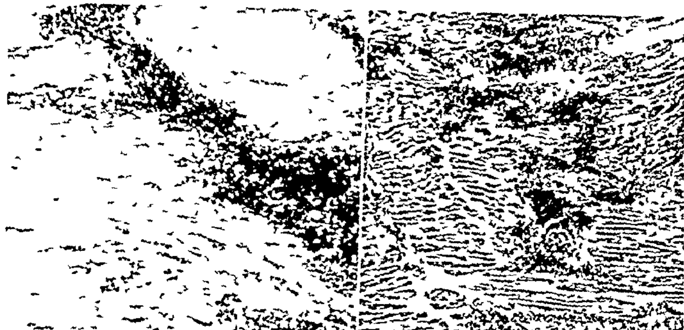


Fig 3 Photomicrographs of hemorrhagic myocardial infarction showing two varieties of interstitial hemorrhage unidirectional *(left)* and multidirectional *(right)* Note that extravasated blood has created false tissue planes that split myocardium Individual acutely ischemic fibers appear darker because of eosinophilia (Hematoxylin and eosin original magnification ×120)



Fig 4 Photomicrographs of acute myocardial infarction *Left* In 2 week old nonhemorrhagic myocardial infarct note removal of necrotic tissue *(left upper quadrant of picture)* by phagocytic macrophages at edge of infarct *Right* In 4 week old hemorrhagic infarct note group of smudgy anuclear necrotic muscle fibers *(in center of picture)* in a sea of red blood cells as yet to be removed (Hematoxylin and eosin original magnification ×200)

of the patients had only single vessel disease

Hemorrhagic myocardial infarction occurred in both transmural and subendocardial infarction Although free perforation had not taken place in any of the infarcts hemorrhage often extended beyond the infarcted zones The extravasated blood formed irregular unidirectional or multidirectional dissecting tracts and created false tissue planes that split the myocardium (Fig 3) Most hemorrhagic infarcts showed an impaired healing process histologically For non hemorrhagic infarcts removal of necrotic muscle by phagocytic leukocytes and the formation of vascular granulation tissue were well under way toward the end

the brain and kidney[3-5] restoration of blood flow after an anoxic period often results in non uniform hypoperfusion of ischemic regions Anox ia induced cellular and interstitial edema is responsible for this phenomenon of no reflow in the microcirculation of the jeopardized tis sue—which of course compounds the deleterious effects of ischemia

The pathogenesis of hemorrhagic myocardial infarction in the patients in Group II is unclear Since aortocoronary bypass predated the is chemic injury hemorrhage cannot be attributed to the direct effect of reperfusion It is possible that the hemorrhage occurs as a complication of cardiopulmonary bypass coincidental to the myocardial infarction that has developed Pre sumably perioperative hemorrhage if present would have resolved by 15 to 90 days after aortocoronary bypass in the patients in Group III

In conclusion immediate revascularization for evolving myocardial infarction although a theo retically attractive concept and surgically feasi ble must be approached with caution because of the prevalence of hemorrhagic myocardial infarc tion and its attendant high mortality rate The two possible exceptions are for patients in whom acute myocardial infarction develops during cardiac catheterization [3] and for those in cardiogenic shock after acute infarction [4] In these desperate situations prompt surgical inter vention may indeed be life saving and may repre sent the treatment of choice The question of optimal management for patients with persistent pain after documented myocardial infarction remains to be answered

Summary

Experimentally hemorrhage and extension of myocardial infarction occur commonly when there is reperfusion after coronary artery occlu sion To investigate this hazard in a clinical setting we compared the histopathologic picture of myocardial infarction in 44 patients who had undergone aortocoronary bypass 14 (Group I) had myocardial infarction that predated aorto coronary bypass by 1 to 7 days 13 (Group II) had infarction 1 to 14 days after the surgery and 17 (Group III) had infarction 15 to 90 days postoper atively All 44 patients had two or more coronary arteries with luminal narrowing of more than 75 per cent and patent vein grafts to arteries supplying areas of infarction Hemorrhagic infarcts were present in 57 per cent of patients (eight of 14) in group I and 38 per cent of patients (five of 13) in Group II contrasting with 6 per cent of patients (one of 17) in Group III ($P < 0.005$ and $P < 0.05$ respectively) In hemor rhagic infarcts the extravasated blood formed irregular intramural dissecting tracts beyond the area of infarction and foci of myocardial necrosis were present in the border zones Infarcts affected more than 50 per cent of the left ventricular muscle in 64 per cent of cases of hemorrhagic infarction and in 13 per cent of cases of nonhem orrhagic infarction ($P < 0.05$) The prevalence of hemorrhagic infarction after revascularization may account for the high mortality of evolving and perioperative myocardial infarction asso ciated with aortocoronary bypass and this finding militates against wholesale immediate revascularization in patients who have uncompli cated myocardial infarction

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hemorrhagic infarcts contrasting with only four of 30 patients (13 per cent) with nonhemorrhagic infarcts ($P < 0.05$). That all patients with an infarct size of 50 per cent or larger had died in pump failure was evident by the finding of severe pulmonary edema at autopsy.

Discussion

After a decade of clinical experience, there is now little or no contradiction to the general belief that aortocoronary bypass surgery usually relieves angina and the 30 day surgical mortality rate in uncomplicated cases is 5 per cent or lower. The late attrition of aortocoronary bypass ranges from 1.5 to 5 per cent per year and this compares favorably with the expected yearly mortality rate of 6 to 18 per cent in a similar group of patients treated medically.

Encouraged by these results, a number of centers have included impending and evolving myocardial infarction as indications for aortocoronary bypass.[2-10] The rationale for immediate revascularization in the early phase of myocardial infarction is to minimize the size of the infarct by increasing perfusion to the ischemic myocardium around the infarct. Experimental studies in dogs killed at varying intervals after coronary artery occlusion have demonstrated a twilight zone of ischemic tissue separating the area of necrosis from the surrounding uncompromised myocardium.

However, reperfusion during evolving myocardial infarction is not a panacea. To be effective, reperfusion must commence within 1 or 2 hours of coronary occlusion,[11,15,25] a deadline that can seldom be met in most clinical situations. Recent experimental findings suggest that indeed revascularization may exacerbate rather than limit myocardial injury. When conscious dogs were subjected to coronary occlusion by constriction of an exteriorized snare for 5 hours, myocardial hemorrhage occured in 44 per cent of the animals when reperfusion was implemented by releasing the occlusive snare. This was accompanied by massive extension of the infarction as reflected by serial changes in serum creatine phosphokinase.[11] In addition, the hemodynamic status of the reperfused animals was significantly worse 2 to 3 hours after reperfusion than that of the control group at corresponding times, and pathologic Q waves indicating transmural infarction developed sooner in the animals undergoing reperfusion.[11,15]

The results of our study indicate that a parallel situation exists in the clinical setting. The risk of developing hemorrhagic myocardial infarction in patients who had infarction 14 days or longer after aortocoronary bypass (6 per cent in Group III) was probably no greater than that in patients without aortocornary bypass. However, hemorrhagic myocardial infarction was almost ten times more common in patients who had evolving myocardial infarction and aortocoronary bypass (57 per cent in Group I) and more than six times commoner in patients who had aortocoronary bypass and perioperative myocardial infarction (38 per cent in Group II). Pathologically, hemorrhagic infarcts showed several features that are prognostically unfavorable for survival, namely delayed healing, extension of ischemic injury to the myocardium, and pump failure.

The prevalence of hemorrhagic infarcts may account for the high mortality of patients who have had evolving and perioperative myocardial infarction associated with aortocornay bypass.[16] Analyzing the data on 1,700 patients who had undergone aortocoronary bypass without additional cardiovascular procedures, Dawson and associates[16] found that the early mortality in patients who had undergone aortocoronary bypass within the first 7 days after acute myocardial infarction (38.1 per cent) was more than six times greater than the mortality in patients who had been operated on 31 to 60 days after acute infarction (5.8 per cent). The result reported by Pifarre and associates[7] were equally alarming: the mortality rate of patients who had undergone aortocoronary bypass at 2½ to 12 hours, 13 to 48 hours, 2 to 13 days, 14 to 30 days and 31 to 60 days was 33 per cent, 100 per cent, 50 per cent, 17 per cent and 0 per cent, respectively.

Hemorrhagic infarction is a reperfusion injury following prolonged myocardial ischemic anoxia. It has been observed before aortocoronary bypass was in vogue in surgical procedures requiring cardiopulmonary bypass. Experimentally, the extent of hemorrhagic necrosis is directly proportional to the duration of the preceding period of ischemic anoxia and the hemorrhage is attributable to anoxic injury to the capillary endothelium.[23,24] In the heart,[11] as in

the brain and kidney[3–5] restoration of blood flow after an anoxic period often results in non uniform hypoperfusion of ischemic regions Anoxia induced cellular and interstitial edema is responsible for this phenomenon of no reflow in the microcirculation of the jeopardized tissue—which of course compounds the deleterious effects of ischemia

The pathogenesis of hemorrhagic myocardial infarction in the patients in Group II is unclear Since aortocoronary bypass predated the ischemic injury hemorrhage cannot be attributed to the direct effect of reperfusion It is possible that the hemorrhage occurs as a complication of cardiopulmonary bypass coincidental to the myocardial infarction that has developed Presumably perioperative hemorrhage if present would have resolved by 15 to 90 days after aortocoronary bypass in the patients in Group III

In conclusion immediate revascularization for evolving myocardial infarction although a theoretically attractive concept and surgically feasible must be approached with caution because of the prevalence of hemorrhagic myocardial infarction and its attendant high mortality rate The two possible exceptions are for patients in whom acute myocardial infarction develops during cardiac catheterization[11] and for those in cardiogenic shock after acute infarction In these desperate situations prompt surgical intervention may indeed be life saving and may represent the treatment of choice The question of optimal management for patients with persistent pain after documented myocardial infarction remains to be answered

Summary

Experimentally hemorrhage and extension of myocardial infarction occur commonly when there is reperfusion after coronary artery occlusion To investigate this hazard in a clinical setting we compared the histopathologic picture of myocardial infarction in 44 patients who had undergone aortocoronary bypass 14 (Group I) had myocardial infarction that predated aortocoronary bypass by 1 to 7 days 13 (Group II) had infarction 1 to 14 days after the surgery and 17 (Group III) had infarction 15 to 90 days postoperatively All 44 patients had two or more coronary arteries with luminal narrowing of more than 75 per cent and patent vein grafts to arteries supplying areas of infarction Hemorrhagic infarcts were present in 57 per cent of patients (eight of 14) in group I and 38 per cent of patients (five of 13) in Group II contrasting with 6 per cent of patients (one of 17) in Group III ($P < 0.005$ and $P < 0.05$ respectively) In hemorrhagic infarcts the extravasated blood formed irregular intramural dissecting tracts beyond the area of infarction and foci of myocardial necrosis were present in the border zones Infarcts affected more than 50 per cent of the left ventricular muscle in 64 per cent of cases of hemorrhagic infarction and in 13 per cent of cases of nonhemorrhagic infarction ($P < 0.05$) The prevalence of hemorrhagic infarction after revascularization may account for the high mortality of evolving and perioperative myocardial infarction associated with aortocoronary bypass and this finding militates against wholesale immediate revascularization in patients who have uncomplicated myocardial infarction

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Long term follow up of aneurysmectomy for recurrent ventricular tachycardia or fibrillation

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The association of life threatening recurrent ventricular tachyarrhythmias and left ventricular aneurysm has been recognized for several years Since Couch first described a case of recurrent ventricular tachycardia abolished by aneurysmectomy there have been numerous reports of such treatment However most studies involved small series or isolated case reports with relatively short follow up periods using end points such as symptoms and the standard resting electrocardiogram The present study describes ten patients whose primary indication for aneurysmectomy was the presence of recurrent ventricular tachyarrhythmias Their long term follow up included a graded exercise test and 24 hour Holter monitoring in order to further evaluate the role of aneurysmectomy in the treatment of recurrent ventricular arrhythmias

Material and methods

Patient material From January 1972 through January 1976 106 patients underwent surgical resection of a saccular aneurysm at the Montreal Heart Institute Of these 10 patients whose primary indication for aneurysmectomy was the presence of recurrent ventricular arrhythmias were selected for study Table I lists the clinical and angiographic features of these patients There were nine men and one woman their mean age was 53 years (Range 26 to 69 years) The aneurysm was caused by myocardial infarction in nine patients and was post traumatic in one patient All patients had symptoms of recurrent ventricular arrhythmias in the preoperative period resistant to standard antiarrhythmic therapy Each arrhythmia was documented on rhythm strips during observation in hospital

The preoperative diagnosis of left ventricular aneurysm was based on biplane left ventricular angiography The angiographic criteria for left ventricular aneurysm included a saccular deformity of the left ventricular cavity which persisted both in systole and diastole The contraction pattern of the remaining myocardium was classified as good when there were no contraction abnormalities in non aneurysmal segments fair when moderate hypokinesis akinesis or dyskinesis was observed in one segment and poor when one of these abnormalities was observed in more than one segment At operation a true saccular aneurysm as defined by Loop was resected in all patients Survivors were reevaluated an average of 22 (4 to 42) months after surgery All had a history and physical examination a resting electrocardiogram a multistage bicycle exercise test and ambulatory 24 hour Holter monitoring The multistage bicycle ergometric test was performed using initial workload of three metabolic equiv

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Work supported in part by the J L Lévesque Foundation
Received for publication July 28, 1977
Accepted for publication Sept. 19 1977
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0002-8703/78/0396-0303$00.60/0 © 1978 The C V Mosby Co

Table I Preoperative clinical and hemodynamic status

		Clinical status			Hemodynamic status				
					Ventriculographic findings			Coronary angiography	
	Age at operation	Type of arrhythmia	Symptoms during arrhythmia	Symptoms between episodes	Aneurysm site	Aneurysm size	Remaining myocardium	No of vessels with stenosis ≥ 50%	Rest LVEDP (mm Hg)
1	51 M	Ventricular fibrillation	Cardiac arrest	Dyspnea Class II*	Anterolateral	Large	Good	1	13
2	55 F	Ventricular tachycardia	Dizziness and palpitation	Dyspnea Class I	Anterolateral diaphragmatic	Large	Fair	2	15
3	60 M	Ventricular tachycardia	Dizziness and palpitation	Asymptomatic	Anterolateral diaphragmatic	Large	Good	1	24
4	56 M	Ventricular tachycardia	Palpitation dyspnea angina hypotension	Asymptomatic	Anterolateral	Large	Fair	3	35
5	58 M	Supraventricular and ventricular tachycardia	Angina	Angina Class II	Posterobasal	Moderate	Good	3	9
6	69 M	Ventricular fibrillation	Cardiac arrest	CHF emboli m	Anterolateral	Large	Poor	1	32
		Ventricular tachycardia	Syncope		Distal septal				
7	26 M	Ventricular tachycardia	Palpitation angina	Asymptomatic	Anterolateral	Moderate	Good	0	6
8	46 M	Ventricular tachycardia	Dizziness palpitation	Asymptomatic	Anterolateral	Large	Good	3	28
9	58 M	Ventricular tachycardia	Palpitation angina	Angina Class II	Anterolateral	Moderate	Good	2	10
10	64 M	Ventricular tachycardia	Dizziness angina	Dyspnea Class II	Anterolateral	Large	Poor	2	30
					Distal-septal				

* New York Heart Association functional classification
Abbreviations LVEDP left ventricular end diastolic pressure F female M male

alents (mets) increasing by one met increments every 2 minutes During exercise and for 5 to 10 minutes thereafter Leads CM_5 and CM_5 were continuously monitored on an oscilloscope and recorded each minute or more often if an arrhythmia was noted The indications for stopping the test are shown in Table II

Ambulatory electrocardiographic monitoring was done with a portable Avionic Electrocardio recorder model 425 with standard disposable silver-silver chloride electrodes employing a modified Lead V_1 and V_5 configuration Each patient kept a diary to record events Analysis of the recordings were done using an Avionic Dynamic Electrocardioscanner model 660 A in a semiautomated manner as described by Lown and associates[1] The electrocardioscanner has a high speed playback analyzer running at 60 or 120 times real time and a low speed paper recorder Audiovisual techniques using an R wave triggered oscilloscopic display and an electrocardiographic coupled sound system enabled detection of ventricular events At the same time normal heart beats and ventricular extrasystoles were automatically counted on a digital computer and were charted hourly Focality of the ventricular extrasystoles were noted as well as the presence of couplets or runs of ventricular tachycardia All ventricular events were rerun at real time speed to verify their nature and number All tapes were

erpreted by two experienced cardiologists and onsensus opinion was reached on the number d type of ventricular arrhythmias

ults

There was no operative mortality Of six atients with multivessel disease three had associated aortocoronary bypass procedures (cases No 2 4 5) Two patients (cases No 6 and 8) died uddenly at 7 and 15 months respectively ollowing operation Neither patient had an associated revascularization procedure and patient No 6 had poor left ventricular contraction in the non aneurysmal myocardium preoperatively The signs and symptoms of the eight survivors are shown in Table II Although seven out of eight patients had persistent palpitations all but one considered themselves symptomatically improved No patient had radiologic evidence of congestive heart failure The resting electrocardiogram showed ventricular extrasystoles in only three out of eight cases whereas the Holter monitor demonstrated multifocal ventricular extrasystoles in all patients and short runs of ventricular tachycardia which were asymptomatic in three patients Exercise increased the number of premature ventricular contractions in three patients Antiarrhythmic medication had been stopped in all but one patient following aneurysmectomy because of symptomatic improvement Table II shows that there was no correlation between recurrence of ventricular arrhythmias and aneurysm size or contraction pattern of non aneurysmal segments or the extent of coronary disease

Discussion

Our results suggest that aneurysmectomy may be beneficial in the treatment of recurrent ventricular tachyarrhythmias However long term follow up using ambulatory Holter monitoring revealed a surprisingly high incidence of persistent serious ventricular arrhythmias which call for a careful patient selection for surgery as well as close follow up of these patients

The over all incidence of arrhythmias in patients with left ventricular aneurysm is not known In our hospital aneurysmectomy was performed in 106 patients during a 3 year period Ten of our patients (9 per cent) had presented serious and/or recurrent ventricular tachyarrhythmias preoperatively and a similar incidence can be found in most other large series However it is possible that a much larger percentage of patients with left ventricular aneurysm experience short runs of ventricular tachycardia which are not symptomatic and are undetected

Several investigators [,] have observed that tachyarrhythmias are more frequent in patients with large aneurysms and virtually absent in patients with small aneurysms Rochemaure and colleagues have also related prognosis to aneurysmal size noting that arrhythmias accounted for seven of eight deaths in their group with large size aneurysms The function of other left ventricular segments as well as the extent of coronary artery disease in the genesis of ventricular tachyarrhythmias is not clear Four patients in our series had important ventricular arrhythmias with single vessel disease and good contraction of non aneurysmal segments Furthermore there are many reported cases of ventricular tachyarrhythmias in patients with a left ventricular aneurysm and normal coronary arteries For these reasons it is difficult to evaluate the coincident role of multiple vessel disease and non aneurysmal segments in the initiation and maintenance of ventricular arrhythmias However multivessel disease may have a bearing on the patient's ability to cope with his arrhythmia as well as on the prognosis of aneurysmectomy if complete revascularization cannot be obtained Of the two patients in our series who died during the follow up period one had poor contraction in left ventricular segments other than the aneurysm and the other had triple vessel disease not suitable for aortocoronary bypass surgery

Role of surgery

Many authors have reported on the beneficial role of aneurysmectomy in the control of ventricular tachyarrhythmias Sixty per cent of our patients were less symptomatic after surgery By removing the saccular aneurysm myocardial efficiency is improved thereby increasing cardiac reserve and reducing symptomatic episodes of tachyarrhythmias However our study has shown that aneurysmectomy does not totally abolish serious ventricular tachyarrhythmias Ricks and colleagues have also shown frequent

Table I Preoperative clinical and hemodynamic status

Age at operation	Clinical status: Type of arrhythmia	Symptoms during arrhythmia	Symptoms between episodes	Hemodynamic status — Ventriculographic findings: Aneurysm site	Aneurysm size	Remaining myocardium	Coronary a[illegible]: No of vessels with stenosis ≥ 50%	Rest LVEDP (mm H[illegible])
1 [illegible]1 M	Ventricular fibrillation	Cardiac arrest	Dyspnea Class II	Anterolateral	Large	Good	1	13
2 5[illegible] F	Ventricular tachycardia	Dizziness and palpitation	Dyspnea Class I	Anterolateral diaphragmatic	Large	Fair	[illegible]	[illegible]
3 60 M	Ventricular tachycardia	Dizziness and palpitation	Asymptomatic	Anterolateral diaphragmatic	Large	Good	1	[illegible]
4 56 M	Ventricular tachycardia	Palpitation dyspnea angina hypotension	Asymptomatic	Anterolateral	Large	Fair	3	[illegible]
5 58 M	Supraventricular and ventricular tachycardia	Angina	Angina Class II	Posterobasal	Moderate	Good	3	9
6 69 M	Ventricular fibrillation	Cardiac arrest	CHF embolism	Anterolateral	Large	Poor	1	3[illegible]
	Ventricular tachycardia	Syncope		Distal-septal				
7 26 M	Ventricular tachycardia	Palpitation angina	Asymptomatic	Anterolateral	Moderate	Good	0	6
8 46 M	Ventricular tachycardia	Dizziness palpitation	Asymptomatic	Anterolateral	Large	Good	3	[illegible]
9 58 M	Ventricular tachycardia	Palpitation angina	Angina Class II	Anterolateral	Moderate	Good	2	10
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				Distal-septal				

New York Heart Association functional classification
Abbreviations LVEDP left ventricular end diastolic pressure F female M male

alents (mets) increasing by one met increments every 2 minutes During exercise and for 5 to 10 minutes thereafter Leads CM and CM_5 were continuously monitored on an oscilloscope and recorded each minute or more often if an arrhythmia was noted The indications for stopping the test are shown in Table II

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excessive stretch and mechanical trauma to the His Purkinje system The marginal zone of most aneurysms is a mixture of healthy tissue and scar and is not totally resected using current surgical techniques If the irritable site was located in the marginal zone of the aneurysm it would explain the persistence of ventricular arrhythmias postoperatively Epicardial mapping and preoperative electrophysiologic studies may become useful techniques in localizing the arrhythmogenic segment(s)

Since complex arrhythmias persist following aneurysm resection the presence of these arrhythmias preoperatively in an asymptomatic or mildly symptomatic patient should not be an indication for surgery The operative mortality rate for aneurysmectomy in several series is reported to be 10 to 20 per cent and there are no data presently available which show that aneurysm resection prolongs life in asymptomatic or mildly symptomatic patients For these reasons aneurysmectomy to control ventricular arrhythmias should be reserved for patients whose symptoms cannot be controlled by antiarrhythmic medication Our results show that all patients who have a ventricular aneurysm resection for ventricular ectopy should have dynamic monitoring postoperatively The presence of complex arrhythmias following aneurysmectomy is an indication for vigorous antiarrhythmic therapy

Summary

The success of aneurysmectomy in abolishing recurrent ventricular tachycardia or ventricular fibrillation has not been clearly defined Ten patients who underwent aneurysm resection to control ventricular arrhythmias were studied before and an average of 19 (4 to 42) months following operation All patients had moderate to large aneurysms and four had asynergy in adjacent segments Of four patients with significant stenosis in vessels not supplying the aneurysm three had aortocoronary bypass grafts in addition to their resection Ambulatory Holter monitoring and a graded exercise test were performed in all patients postoperatively

There was no operative mortality Two patients who did not have associated revascularization procedures died suddenly 15 and 7 months postoperatively Of the eight survivors despite clinical improvement the Holter ECG revealed runs of ventricular tachycardia in three patients and frequent multifocal ventricular extrasystoles in the other five patients No correlation was found between recurrence of the ventricular arrhythmias and aneurysm size contraction pattern of other myocardial segments extent of coronary disease or the presence of congestive heart failure

In conclusion aneurysmectomy does not abolish ventricular tachyarrhythmias and probably should be reserved for patients who remain symptomatic despite an adequate medical trial The persistence of complex arrhythmias following operation warrants a close follow up in these patients

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Table II Follow up of surviving patients

Pt no	Clinical aspects				Holter monitoring		Multistage bicycle ergometric test			
	Time of post op follow up	*Symptoms*	*Medication at time of follow up*	*Resting ECG*	*Total no of HB*	*Ventricular arrhythmias*	*Indication for stopping*	*Peak HR*	*ST depression ≥ 1 mm*	*Ventricular arrhythmias*
1	42 mos	Palpitations	Quinidine bisulfate 400 mg/d	No arrythmias	99594	168 multifocal PVBs 1 couplet in 21 h	Dyspnea	130 (78% of MPHR)	Absent	Multifocal PVBs > 1/10 HB ↑ with effort
2	40 mos	Palpitations orthopnea	Digoxin 0.25 mg/d Furosemide 40 mg/d	No arrhythmias	99367	112 multifocal PVBs 1 ventricular tachycardia in 23 h	Angina	130 (80% of MPHR)	Present	None
7	28 mos	Palpitations	None	Unifocal PVBs < 1/10 HB	133353	2000 multifocal PVBs > 10 couplets in 23 h	End point	142 (90% of MPHR)	Absent	Unifocal PVBs < 1/10 HB no ↑ with effort
4	24 mos	Dizziness dyspnea Class II* orthopnea	Digoxin 0.25 mg/d Furosemide 40 mg/d	Multifocal PVBs > 1/10 HB	101488	4700 multifocal PBVs in 22 h	Exhaustion	140 (85% of MPHR)	Absent	Multifocal PVBs < 1/10 HB no ↑ with effort
5	21 mos	Palpitations angina Class II dizziness	Digoxin 0.25 mg/d Furosemide 60 mg/d Propranolol 60 mg/d	Multifocal PVBs < 1/10 HB	103982	4890 multifocal PVBs > 10 couplets 1 ventricular tachycardia in 23 h	Angina	120 (75% of MPHR)	Present	Multifocal PVBs > 1/10 HB couplets ↑ with effort
7	12 mos	Palpitations	None	No arrhythmias	129417	153 multifocal PVBs in 24 h	End point	190 (90% of MPHR)	Absent	None
9	5 mos	Angina at rest syncope palpitations orthopnea	None	No arrhythmias	129792	69 multifocal PVBs 1 ventricular tachycardia in 23 h	End point	148 (90% of MPHR)	Absent	None
10	4 mos	Asymptomatic	None	No arrhythmias	127421	300 multifocal PVBs in 24 h	End point	142 (90% of MPHR)	Absent	None

*NYHA functional classification
HB = heart beats MPHR = maximal predicted heart rate PVBs = premature ventricular beats

ventricular irritability in eight of 12 patients following aneurysm resection performed to abolish ventricular arrhythmias The focus of irritability following aneurysm formation could be caused by reentrant arrhythmias arising from decreased velocity of conduction through scar tissue variable refractory periods of ischemic and non ischemic tissue non uniform repolarization of tissue bordering the aneurysm and/or enhanced automaticity caused by ischemia

Coronary ectasia: Incidence and results of coronary bypass surgery

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Localized or diffuse coronary artery dilatation with or without coronary artery stenosis has been called aneurysm by some authors[1] and ectasia by others.[1] Most of these coronary abnormalities have been considered atherosclerotic and/or congenital[1] in origin. Others have been attributed to bacterial infection, syphilis, septic embolism, trauma, dissection,[5] or have been described in association with polyarteritis nodosa,[8] scleroderma, Ehlers-Danlos syndrome, Takayasu's arteriopathy, Marfan's syndrome, and metastatic tumor. After the first autopsy reports of coronary dilatation by Morgagni in 1761 and by Gougon in 1812, approximately 164 more cases of coronary aneurysm have appeared in the literature. The antemortem diagnosis of coronary aneurysm has been reported in only 9? patients and of those 36 have undergone resection of the aneurysm or saphenous vein bypass surgery. In one reported series, the short term prognosis of coronary ectasia was observed to be poor with a yearly mortality rate of 15 per cent.

In order to evaluate the significance of coronary ectasia and the result of saphenous vein bypass graft in this group, we reviewed our experience in 42 patients with coronary ectasia, of whom 30 underwent bypass grafting.

Material and methods

Between January 1974 and December 1976, 1,660 patients underwent coronary angiography for chest pain or shortness of breath at the Long Island Jewish-Hillside Medical Center. In all patients right and left cardiac catheterization and selective coronary angiography was performed either by the Judkins or Sones techniques using the General Electric image intensification system recorded on 35 mm film at 60 frames/sec. In quantitating left ventricular dysfunction and the pattern of left ventricular contraction, the same techniques and principles were used as previously reported,[7] utilizing the descriptive terminology suggested by Herman and associates.[38] Coronary arteries with at least 50 per cent reduction in diameter were considered *significantly stenosed* and were bypassed whenever feasible in patients with exertional or resting angina pectoris. No patients with coronary ectasia underwent coronary bypass surgery unless one or more of their coronary arteries demonstrated at least 50 per cent reduction in diameter. The severity and extent of coronary disease were graded according to the criteria of Bruschke and associates.[39] Postbypass recatheterization and angiography were done 10 to 15 days after surgery in order to assess the patency of the grafts and any change in left ventricular function. The electrocardiographic criteria for the diagnosis of myocardial infarction were those of Class 1 1 and 1 2 of the Minnesota code reported by Blackburn and associates.[40] All

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Received for publication Aug. 16, 1977.
Accepted for publication Oct. [illegible]0, 19[illegible].

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Among the 1 660 patients 42 (2 5 per cent) had ... iary ectasia Twenty five patients were over age 50 and 17 under This study did not include patients with coronary aneurysmal dilatation secondary to coronary arterovenous fistulae or fistulae between coronary arteries and cardiac chambers The 42 patients with coronary ectasia were matched for age and sex with a control group also referred for symptomatic coronary artery disease Thirty patients with coronary ectasia and 27 patients in the control group underwent aortocoronary bypass surgery Post operatively angiograms were performed in 19 patients in the ectasia group and in 17 controls

Results

Of 42 patients with coronary ectasia 25 had resting angina 15 exertional angina and two young patients were asymptomatic and had coronary angiography because of strongly positive stress tests after recent myocardial infarction There was no significant difference (Table I) between the clinical profile when ectasia and control groups were compared Comparison between the groups for the number of vessels involved the frequency of left main coronary artery disease and segmental abnormal wall motion revealed no differences (Table I) The mean serum cholesterol level was 240 ± 75 and 250 ± 45 mg /100 ml in the ectasia and control groups respectively while the triglyceride level was 224 ± 106 in the ectasia and 170 ± 68 mg / 100 ml in the control group ($p < 0025$) Three patients with ectasia had significant aortic valvular disease (two aortic insufficiency and one aortic stenosis) Coronary calcification was equally distributed in patients with (70 per cent) or without (80 per cent) ectasia

Of 64 ectatic vessels in 42 patients 34 (53 per cent) occurred in the right coronary 16 (25 per cent) in the left anterior descending artery and 14 (22 per cent) in the circumflex artery (Table II) Only 39 of 64 (61 per cent) ectatic coronary arteries had luminal narrowing exceeding 50 per cent In affected vessels diffuse ectasia was noted in 85 per cent of right 71 per cent of circumflex and 50 per cent of left anterior descending arteries Type III ectasia was noted mostly in the right coronary artery (Table II)

Coronary bypass surgery and post surgical follow up Saphenous vein bypass surgery was performed in 30 patients with coronary ectasia and in 27 controls Two week post bypass angiograms were performed in 19 of 30 (63 per cent) patients with ectasia and in 17 of 27 (63 per cent) control patients Of the 46 bypass grafts studied postoperatively in the ectasia group two (4 per cent) were closed while five of 41 (12 per cent) were closed in the non ectaisa control group There were no deaths in any surgical patients with or without ectasia In two patients of each group new Q waves developed postoperatively and three patients of the ectasia group and two controls had recurrent angina pectoris after bypass Of 12 patients with ectasia who did not have surgery three had coronary stenosis less than 50 per cent five were not considered candidates for surgery because of diffuse double or triple vessel involvement while the remaining four had single vessel disease In the non operated controls four patients had coronary stenosis less than 50 per cent four had isolated single vessel disease and of the remaining seven patients two refused surgery while five had diffuse coronary disease judged not amenable to bypass surgery One of the patients with a 60 to 90 per cent stenosis of an ectatic right coronary artery (Fig 3) developed inferior wall infarction one year after his initial angiogram but subsequently underwent double vessel bypass surgery for progressive angina

TYPE III



Fig 3 Type III ectasia In a patient with severe triple vessel coronary disease only right coronary artery was diffusely ectatic and had significant stenosis of the vessel at the level of the crux (arrow)

In a mean follow up period of 18 months no deaths occurred in the ectasia group while one

TYPE I

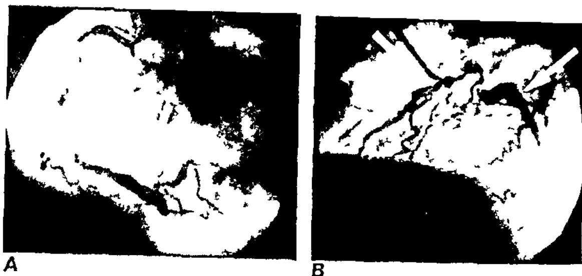


Fig 1 Type I ectasia coronary angiogram of a patient with diffuse ectasia of right *(A)* and circumflex artery *(B)* with localized ectasia and significant proximal stenosis of the left anterior descending artery *(B)*

TYPE II

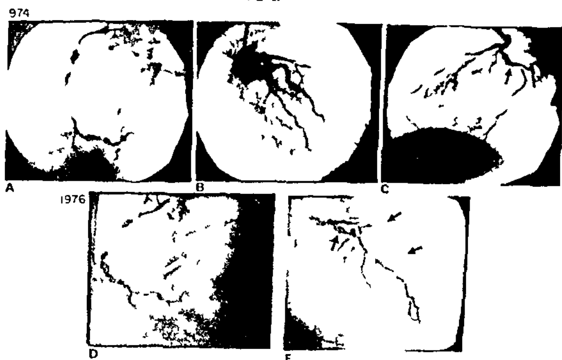


Fig 2 Type II ectasia coronary angiogram of 32 year old male performed in 1974 showing diffuse ectasia and significant narrowing *(arrow)* of the right coronary artery *(A)* with localized ectasia of circumflex artery *(arrow in C)* A year after this study he sustained a transmural inferior wall infarction Two years later repeat coronary angiogram showed progression of disea e not only on the right coronary *(arrow in D)* but also on main left *(white arrow in E)* and left anterior descending arteries *(upper black arrows in E)*

the angiograms were reviewed by two cardiologists (A A and R I H) and coronary ectasia was diagnosed In this study *localized or diffuse* dilatation of a coronary artery is designated as ectasia rather than aneurysm since most of our patients had associated coronary stenosis while none had a past history suggestive of polyarteritis nodosa trauma or penetrating chest wounds Coronary ectasia was *defined* as a localized or diffuse coronary dilatation at least one and one half times the diameter of the patient s largest vessel *Ectasia was classified according to the* criteria of Markis and colleagues [1] Type I (Fig 1) consisted of diffuse ectasia of two or three vessels Type II (Fig 2) diffuse ectasia of one and localized ectasia of another Type III (Fig 3) diffuse ectasia of only one vessel Type IV (Fig 4) localized or segmental ectasia of one vessel

Table I Clinical profile and extent of coronary disease

	Coronary ectasia	Control group
Patients (No)	42	42
Hypertension	10	17
Abnormal glucose tolerance	18	20
Family history		
Coronary artery disease	26	29
Hypertension	14	20
Diabetes	13	8
Electrocardiogram		
Normal	19	21
Inferior infarction	13	13
Anterior infarction	8	7
Left ventricular hypertrophy	4	1
Number of vessels involved		
Single	11	10
Double	11	12
Triple	16	18
Main left	3	4
< 50% Stenosis	4	2
Left ventricular wall motion		
Normal	13	10
Abnormal		
One wall	21	22
Two walls	8	10

Table II Type and extent of coronary ectasia

	Total	Type I	Type II	Type III	Type IV
Number	42	9	8	14	11
Ectasia RCA	34	9	7	13	5
Ectasia LAD	16	7	6	0	3
Ectasia CX	14	7	3	1	3
Valve surgery	3	0	0	0	3
Bypass surgery (pts)	30	7	4	9	10
Grafts placed	67	16	7	18	16
Grafts studied	47	14	6	15	12
Closed grafts	2	1	0	1	0
Deaths	0	0	0	0	0
Postop new Q waves	2	1	0	1	0

Abbreviations RCA = right coronary artery LAD = left anterior descending artery CX = left circumflex artery

and colleagues[15] both considered hypertension to be an important factor in the pathogenesis of this entity but could not explain why other patients with hypertension did not develop ectatic coronaries Microscopic examination of the ectatic vessels revealed massive destruction of the muscular elements of the media at times with inflammatory reaction and focal calcium deposits as well as subintimal fibrosis with deposition of lipoid material It is conceivable that the primary abnormality in these patients is a congenital abnormality of the arterial wall with superimposed metabolic derangement The higher serum triglyceride levels noted in these patients may play a role in the genesis of the lesions In our series the presence of transmural myocardial infarction in the electrocardiogram was just as frequent in patients with (50 per cent) or without (48 per cent) ectasia whereas in the Markis and colleagues series (14) patients with ectasia had a higher incidence of electrocardiographic evidence of transmural infarction (80 per cent) than did controls (46 per cent) Unlike Markis and colleagues we found no difference in the family history of coronary artery disease in patients with or without ectasia (Table I) In the ectasia group four patients met electrocardiographic criteria for left ventricular hypertrophy compared to only one in the control group However in three of these four patients the electrocardiographic changes were due to severe aortic valvular disease requiring surgery (one rheumatic and the other two tricuspid calcific valves) The only difference between the patients with or without coronary ectasia was a higher mean serum triglyceride level in the ectasia group

The causes of death in previously reported patients with coronary ectasia has been rupture of an abdominal aneurysm[4] or thrombosis or rupture of a coronary aneurysm [19] [1] Myocardial infarction was attributed to thrombosis in the aneurysm or embolization of thrombus from the aneurysmal sac to the distal coronary artery[3 3]

Since the first report of bypass surgery in a patient with coronary aneurysm or ectasia 34 more cases have been reported in the literature with four deaths [0 26 3 34 3] None of our 42 patients with coronary ectasia who did or did not undergo coronary bypass surgery died in a mean follow up period of 18 months One patient in the control group died while waiting at home for triple bypass surgery These results are different from those of Markis and colleagues[1] who reported a 15 per cent yearly mortality rate in a mean follow up period of 24 months in 20 patients with coronary ectasia treated medically In the surgically treated group with coronary ectasia the incidence of perioperative new Q waves early

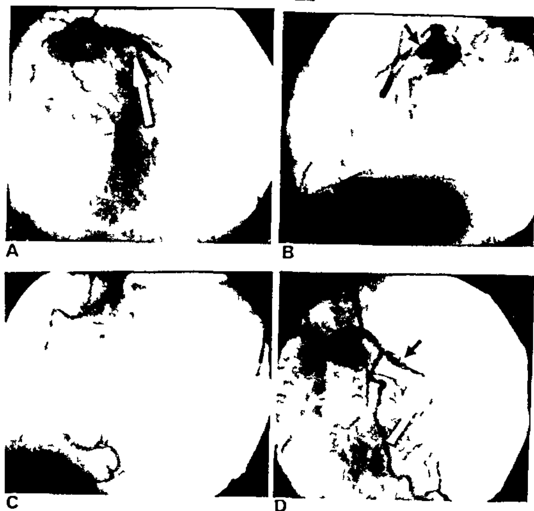


Fig 4 Type IV ectasia Here are shown left coronary angiograms of three different patients with localized ectasia of proximal portion of left anterior descending artery (*white arrow in A and black arrows in B and D*) with significant narrowings distal to the ectasia (*white arrows in B and D*) In the fourth patient (*C*) the localized ectasia is located at the level of the crux (*lower arrow*) with slight narrowing of the proximal right coronary artery (*upper arrow*)

control patient died while waiting at home for elective bypass surgery

Discussion

In 1929 Packard and Wechsler[1] reviewed the literature on 22 autopsy cases of fusiform or saccular coronary aneurysm and added their own case of ruptured left coronary aneurysm According to them most of these aneurysms were of mycotic embolic or arteriosclerotic origin Scott reviewed 46 reported cases and added one of his own Of those only 34 per cent of coronary ectasias occurred in the right coronary artery whereas 64 per cent involved the left coronary system Most of these coronary aneurysms were considered of congenital or mycotic embolic origin Davoud and colleagues [4] in 1963 compiled 79 cases of coronary ectasia and added 10 cases collected from 694 (1 5 per cent) autopsies over a 2½ year period In their 10 cases 66 per cent of ectasias were noted in the right coronary and 34 per cent in the left coronary system In our series the over all incidence of coronary ectasia was 2 5 per cent and occurred twice as often in the right coronary artery (53 per cent) than in the left anterior descending (25 per cent) or circumflex arteries (22 per cent)

In the series of Davoud and colleagues six of 10 patients had a history of hypertension and eight died as a result of abdominal aneurysms Markis and associates [1] as well as Befeler and co workers[11] also noted a high incidence of a history of hypertension in patients with coronary ectasia In our series the incidence of hypertension was the same in patients with or without ectasia (Table I) and those with ectasia did not have obvious clinical signs or symptons of abdominal aneurysm Markis and associates[1] and Durairaj

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closure of bypass grafts and recurrence of angina pectoris was not different from controls

In conclusion coronary ectasia is more common in the right coronary artery, and is mostly of the diffuse type The presence of coronary ectasia does not indicate unusually severe or widespread coronary disease and that short term follow up of patients with coronary ectasia with or without bypass surgery, does not differ from control patients

Summary

Coronary angiograms were performed in 1,660 patients between the ages of 27 and 84 years Coronary ectasia was noted in 42 (2 5 per cent) patients These 42 patients were compared with an equal number of patients with coronary artery disease matched for age and sex There were no significant differences in numbers of vessels involved with significant disease coronary score main left or left anterior descending artery disease, coronary calcification hypertension or abnormal glucose tolerance test in patients with or without ectasia A family history of coronary artery disease diabetes mellitus, and hypertension did not separate the groups neither did serum cholesterol level The serum level of triglyceride was higher in the coronary ectasia group ($p < 0.025$) The location of infarction by electrocardiogram or abnormal left ventricular contractility was similar in both groups Of 64 ectatic vessels 34 (53 per cent) occurred in the right coronary, 16 (25 per cent) in the left anterior descending and 14 (22 per cent) in the left circumflex artery Thirty patients with ectasia and 26 in the control group underwent bypass surgery Nineteen of the ectasia group and 17 of the control group had post bypass graft angiograms In the ectasia group, two out of 47 and in the control group five out of 41 grafts were closed The postoperative course was similar in both groups An 18 month (mean) follow up of the 42 patients with coronary ectasia revealed no late deaths whereas one death occurred in a control patient who did not have surgery In conclusion, coronary ectasia is more common in the right coronary artery The presence of coronary ectasia does not indicate more severe or widespread coronary disease than in controls Short term follow up of patients with ectasia with or without bypass surgery does not differ from control patients

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Table II Antegrade refractory period data

Pt no	CL	ERP of Atrium		ERP of A V node		FRP of A V node		RRP Ab of HPS		RRP HV of HPS		ERP of HPS		FRP of HPS		Gap in A V conduction	
		Con trol	30 min	Con trol	30 min	Con trol	30 min	Con trol	30 min	Con trol	30 min	Con trol	30 min	Con trol	30 min	Cont ol	30 min
1	800	270	80	–	–	350	310	425	425	445	445	410	390	450	440	–	–
	700	2 0	2 0	–	–	355	345	400	410	405	415	385	395	415	420	–	–
	600	280	260	–	–	340	345	375	375	385	390	365	360	385	395	–	–
2	900	350	320	–	–	465	425	–	–	500	500	490	490	505	500	–	–
	850	330	320	–	–	4 5	470	–	–	490	490	485	485	490	490	–	–
3	750	240	250	–	–	355	340	420	415	4 0	415	365	365	425	410	Types I & II	Type I
	650	250	230	–	–	340	340	400	395	400	395	355	350	395	400	Type I	–
4	800	280	270	–	–	395	380	510	510	470	470	430	440	475	480	–	–
5	700	280	< 310	–	–	365	355	420	415	390	370	380	360	390	390	–	–
6	800	260	260	–	–	335	370	430	445	430	445	390	415	435	450	–	–
	700	270	250	–	–	360	360	410	410	410	410	380	380	415	4 0	–	–
7	1000	270	290	–	–	380	370	440	440	445	445	420	420	465	475	–	–
	800	240	300	–	–	370	360	415	415	420	415	400	400	430	430	–	–
	700	250	310	–	–	3 0	350	–	–	400	410	380	380	405	410	–	–
8	700	230	240	–	–	375	355	–	–	440		435	440	445	445	Types I & II	Types I & II
	600	230	250	–	–	345	340	–	–	410	395	405	390	405	405	Type II	Type II
9	900	290	< 350	–	–	390	< 395	480	470	480	470	415	400	450	430	–	–
	800	300	290	–	–	390	380	435	430	435	430	395	395	430	430	–	–
10	800	230	250	–	–	405	405	445	445	430	430	405	420	430	430	Type I	Type I
11	750	290	260	–	–	380	370	460	460	460	460	435	440	455	475	Type I & II	Type II
12	900	270	240	–	–	380	395	–	–	450	450	410	425	460	460	Type I	Type I
	800	250	250	280	300	385	390	–	–	440	440	395	400	435	450	Type I	Type I
13	50	240	270	340	320	405	390	440	440	440	440	430	430	445	450	None	Type I
14	5 0	220	220			305	310	355	355	355	355	31	315	340	335	Type II	Type II

All measurements are in milliseconds
Abbreviations CL = cycle length HPS = His Purkinje system AVN = atrioventricular node ERP = effective refractory period FRP = functional refractory period RRP Ab = relative refractory period of HPS determined by QRS aberration RRP HV = relative refractory period of HPS determined by HV prolongation

trograms as well as electrocardiographic Leads I II III V and time lines generated at 10 and 100 msec were simultaneously displayed on a multichannel oscilloscope and relayed to a magnetic tape recorder Records were later reproduced at a paper speed of 150 mm/sec Careful attention was paid to the grounding of all equipment Measurements of A V nodal and His Purkinje conduction times were made during sinus rhythm and at atrial paced rates up to a maximum of 200 beats/minute

Using the atrial extrastimulus method[3] refractory periods of the atrium A V node and HPS were determined at one or more paced cycle lengths in each patient

Effective refractory period of HPS could be determined in 22 out of 254 consecutive patients in whom antegrade refractory periods were performed In 14 out of 22 patients repeat studies were performed at comparable cycle lengths after a period of 30 minutes

In no patient were the characteristics of the delivered stimuli changed during the course of the study An intravenous line was started with 5 per cent dextrose in all patients at the beginning of the study to stimulate drug studies Blood pressure determinations were made at the beginning of the study and at the completion of the 30 minute studies Statistical analyses were performed using the Student s paired t test

Definition of terms

A H interval was measured from the onset of low atrial electrogram to the onset of His bundle deflection and was taken as an approximation of A V nodal conduction time (normal values for our lab are 60 to 140 msec)

H V interval representing His Purkinje con

Study of the temporal effects on conduction and refractoriness of the His-Purkinje system in man

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The effect of time on refractoriness of the atrium and atrioventricular node have been previously described [1] However, insufficient data are available concerning temporal effects on refractoriness within the His Purkinje System (HPS) Such data are essential in evaluating those antiarrhythmic agents whose primary effect is on the HPS The present report concerns observations made in a prospective study on temporal effects on the relative refractory period (RRP) effective refractory period (ERP), and functional refractory period (FRP) in a group of 14 patients over a 30 minute period

Methods

Electrophysiological studies were performed in the postabsorptive nonsedated state The nature of the study was explained and a signed consent was obtained No patient was receiving cardioactive drugs at the time of study Bundle of His electrograms were recorded as previously described using a tri or quadripolar electrode catheter introduced percutaneously into the right femoral vein and fluoroscopically positioned in the region of the tricuspid valve [2] A No 7 quadripolar catheter was introduced into the antecubital vein and advanced to the high right atrium near its junction with the superior vena cava The distal pair of electrodes were used to stimulate the atrium and the proximal pair to record high right atrial electrogram In addition in some patients a No 6 quadripolar electrode catheter was positioned at the right ventricular apex for ventricular stimulation and recording of local ventricular activity Atrial stimulation was performed using a programmed digital stimulator which delivered rectangular impulses of 1 5 msec duration at a minimum milliamperage which allowed reliable atrial capture Intra cardiac elec

Table I Clinical data

Pt no	*Age*	*Sex*	*Clinical diagnosis*	*ECG diagnosis*
1	40	M	NHD	Normal
2	68	M	ASHD	RBBB LAD
3	29	M	NHD	VPBs LAD
4	28	M	NHD	Incomplete RBBB
5	62	M	NHD	APBs
6	41	M	NHD	Normal
7	58	M	ASHD	Sinus bradycardia
8	62	M	ASHD	RBBB LAD
9	62	M	ASHD	RBBB LAD APB
10	55	M	NHD	RBB LAD APBs
11	45	M	ASHD	LAD
12	60	M	ASHD	VPBs
13	49	M	NHD	VPBs
14	51	M	NHD	VPBs

Abbreviations NHD no heart disease ASHD atherosclerotic heart disease RBBB right bundle branch block LAD left axis deviation VPBs ventricular premature beats APBs atrial premature beats

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This work was supported in part by the Bureau of Medical Services National Heart Lung and Blood Institute Project HL 12436 06

Received for publication Aug 29 1977

Accepted for publication Oct 25 1977

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0002 8703/78/0396 0316$01 00/0 © 1978 T [illegible] Co

ble II Antegrade refractory period data

Pt no	CL	ERP of Atrium		ERP of A V node		FRP of A V node		RRP Ab of HPS		RRP HV of HPS		ERP of HPS		FRP of HPS		Gap in A V conduction	
		Con trol	30 min	Con trol	30 min	Con trol	30 min	Con trol	30 min	Con trol	30 min	Con trol	30 min	Con trol	30 min	Control	30 min
1	800	2,0	280	–	–	350	340	425	4?5	445	445	410	390	450	440	–	–
	,00	2,0	?,0	–	–	355	,45	400	410	405	415	385	395	415	4?0	–	–
	600	280	260	–	–	340	,45	375	3,5	385	390	365	360	38,	395	–	–
2	900	350	320	–	–	465	425	–	–	500	500	490	490	505	500	–	–
	850	330	3?0	–	–	4,5	4?0	–	–	490	490	485	485	490	490	–	–
3	750	240	250	–	–	355	340	420	415	4 0	415	365	365	4?5	410	Types I & II	Type I
	650	2,0	230	–	–	340	340	400	395	400	395	355	350	395	400	Type I	–
4	800	280	270	–	–	395	380	510	510	4,0	4,0	430	440	47,	480	–	–
5	,00	280	< 310	–	–	365	355	4?0	415	,90	3,0	380	360	390	390	–	–
6	800	260	?60	–	–	335	370	430	445	430	445	390	415	435	450	–	–
	700	2 0	250	–	–	360	360	410	410	410	410	380	380	415	4?0	–	–
7	1 000	2 0	290	–	–	380	370	440	440	445	445	420	4?0	465	475	–	–
	800	240	300	–	–	370	360	415	415	4?0	415	400	400	430	430	–	–
	700	250	310	–	–	3?0	3,0	–	–	400	410	380	380	405	410	–	–
8	700	230	?40	–	–	375	3,5	–	–	440		435	440	445	445	Types I & II	Types I & II
	600	230	250	–	–	345	340	–	–	410	395	405	390	405	405	Type II	Type II
9	9?0	290	< 350	–	–	390	< 395	480	4 0	480	4 0	415	400	4,0	430	–	–
	8?0	300	290	–	–	,90	380	435	430	435	430	395	39,	430	430	–	–
10	800	2 0	250	–	–	405	405	445	445	430	430	405	4?0	430	430	Type I	Type I
11	50	290	?60	–	–	380	370	460	460	460	460	435	440	455	475	Type I & II	Type II
12	900	2?0	240	–	–	380	395	–	–	450	450	410	425	460	460	Type I	Type I
	800	2,0	250	280	300	385	390	–	–	440	440	395	400	43,	450	Type I	Type I
13	7,0	240	2?0	340	320	405	390	440	440	440	440	430	430	445	450	None	Type I
14	5,0	2?0	220			305	310	355	355	355	355	315	315	340	335	Type II	Type II

All meas rem ts re in m lliseco ds.
Abbreviati ns CL = cycle lengtl HPS = His P k nje system AVN = trio ntricula node ERP = eff ctive refractory period FRP = funct nal refract ry period RRP Ab = lati e refractory period of HPS det rmined by QRS berration RRP HV = relat e refract y period of HPS determined by HV prolongat n

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Definition of terms

A H interval was measured from the onset of low atrial electrogram to the onset of His bundle deflection and was taken as an approximation of A V nodal conduction time (normal values for our lab are 60 to 140 msec)

H V interval representing His Purkinje con

Table III Cumulative data

Parameter	Control mean ± SD	30 min later mean ± SD	Change	P	Mean absolute change ± SD
Sinus rate	71 ± 11	72 ± 11 5	↑ 1 2	NS	3 4 ± 2 2
A H interval sinus	77 ± 14	76 ± 14	↓ 1 0	NS	1 4 ± 2 3
H V interval sinus	48 5 ± 6 5	48 5 ± 6 5	–	–	–
AVN Wenckebach block (beats/min)	175 ± 18	181 ± 12	↑ 6 0	NS	9 9 ± 11 3
FRP of atrium	264 ± 32	265 ± 30	↑ 1 0	NS	18 6 ± 16 4
FRP of A V node	374 ± 36	366 ± 28	↓ 8 0	<0 05	12 6 ± 11
RRP Ab of HPS	427 ± 37	426 ± 36	↓ 1 0	NS	3 3 ± 4 6
RRP HV of HPS	431 ± 35	430 ± 36	↓ 1 0	NS	4 5 ± 6
FRP of HPS	403 ± 38	401 ± 40	↓ 2 0	NS	7 9 ± 9 1
FRP of HPS	432 ± 36	434 ± 37	↑ 2 0	NS	6 4 ± 6 5

The measurements of conduction time intervals and refractory period measurements are in milliseconds
Abbreviations A H interval = an approximation of A V nodal conduction time H V interval = His Purkinje conduction time ERP = effective refractory period FRP = functional refractory period RRP Ab = relative refractory period determined by QRS aberration RRP HV = relative refractory period determined by H V prolongation NS = not significant at 0 05 level of confidence
↑ = increase
↓ = decrease
= represents average value of change irrespective of its direction

Table IV Conduction studies

Pt no	Sinus rhythm Control			Sinus rhythm 30 min later			Onset of AVN Wenckebach block (beats/min)	
	HR	AH	HV	HR	AH	HV	Control	30 min later
1	67	100	45	71	95	45	190	190
2	69	80	55	62	75	55	130	150
3	68	80	45	68	80	45	190	200
4	75	85	45	77	80	45	190	180
5	85	60	40	92	60	40	175	180
6	71	95	50	69	95	50	185	185
7	58	50	40	55	50	40	175	185
8	73	60	60	77	60	60	180	180
9	65	70	50	67	70	50	175	185
10	60	75	50	63	75	50	None done	
11	69	90	60	69	90	60	170	170
12	67	85	45	63	90	45	190	175
13	80	70	50	82	70	50	150	190
14	100	80	45	96	80	45	1 1 conduction up to 200	1 1 conduction up to 200

Abbreviations HR = heart rate A H interval = an approximation of A V nodal conduction time H V interval = His Purkinje conduction
AVN = atrioventricular node

duction time was measured from the onset of the His bundle deflection to the earliest point of ventricular activation as observed on the ECG tracing or the local ventricular electrogram (normal values for our lab are 30 to 55 msec)

S_1 A_1 H_1 *and* V_1 represent the stimulus artifact atrial, His bundle and ventricular electrogram of the basic atrial drive beats respectively

S_2 A_2 H *and* V represent the stimulus artifact atrial, His bundle and ventricular electrograms of the atrial premature beats respectiv $A_1 A_1$ represents basic paced atrial cycle lengt

Effective refractory period (ERP) of the atriu is the longest S_1S interval at which S does n evoke an atrial response

ERP of the A V node is the longest A interval at which A fails to depolarize the bun of His

ERP of the HPS is the longest H_1H_2 interval which H does not propagate to the ventricle

Functional Refractory Period (FRP) of the A

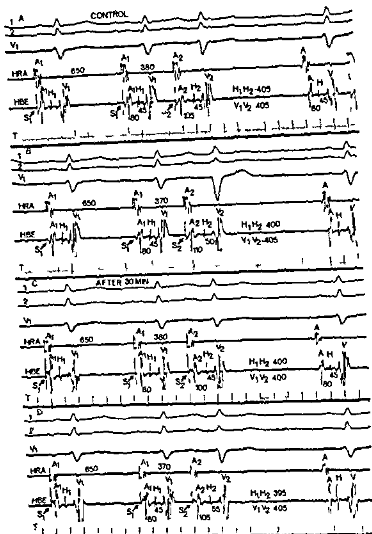


Fig 1 Patient No 3 Relative Refractory Period (RRP HV and RRP Ab) of HPS Each panel shows *from top to bottom* standard electrocardiographic Lead I II V high right atrial electrogram *(HRA)* His bundle electrogram *(HBE)* and time lines *(T)* recorded at 10 and 100 msec *S* = stimulus artifact Similar abbreviations will be used in subsequent figures. The basic cycle length measures 650 *msec and is constant* in all panels In the control period *(panel A)* at a coupling interval (A_1A_2) of 380 msec A_2 conducts to the ventricles with an H_1H_2 interval of 405 msec with minor aberration of QRS morphology but an *unchanged H V* interval compared to basic drive beats At a closer A_1A_2 intervals of 370 msec *(panel B)* A_2 conducts with an H_1H_2 interval of 400 msec and results in incomplete left bundle branch block aberration and prolonged H V interval The H_1H_2 interval of 400 msec defines RRP Ab and RRP HV of HPS During the repeat *study after* 30 minutes at an A_1A_2 interval of 380 msec *(panel C)* A_2 conducts with an H_1H_2 interval of 400 msec No H V prolongation or QRS aberration are seen At a closer coupling interval *(panel D)* the resulting H_1H_2 interval *measures* 395 msec and A_2 conducts with a long H V interval *and* minor aberration Note the decrease of 5 msec in RRP of HPS

node is the shortest H_1H_2 interval in response to any A_1A_2 The FRP of the A V node can only be determined when it is not limited by atrial refractoriness

FRP of the HPS is the shortest V_1V_2 interval in response to any range of H_1H_2 intervals The FRP of the HPS can only be determined when it exceeds the FRP of the A V *node* Therefore at a certain range of H_1H_2 intervals H_2 must be associated with longer H_2V_2 intervals than those of the basic drive beats (H_1V_1)

Relative refractory period (RRP) of HPS is generally defined as the longest H_1H_2 interval at which H_2 conducts to the ventricles with a longer H V interval than the basic drive beat or results in an aberrant QRS complex The detection of minor degrees of aberrant ventricular conduction was more difficult and was subject to greater

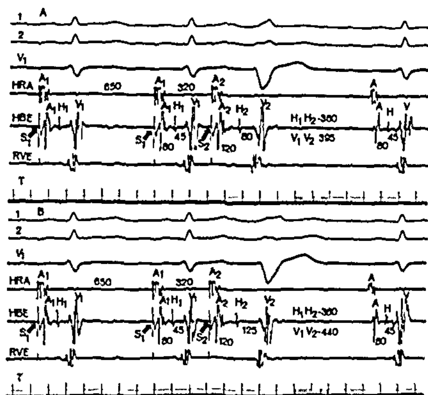


Fig 2 Patient No 3 H_1H_2 intervals vs H_2V_2 intervals during control study The basic cycle length is constant at 650 msec in both panels *In panel A* at an A_1A_2 interval of 320 msec the resulting H_1H_2 interval is 360 msec and A_2 conducts with an H_2V_2 interval of 80 msec and complete left bundle branch block aberration *In panel B* at comparable A_1A_2 and H_1H_2 intervals the resulting H_2V_2 measures 125 msec and aberration is more pronounced In this patient similar changes in H V intervals at comparable H H intervals were present during repeat studies *RVE* = right ventricular electrogram

observer error Therefore for the purpose of this study the longest H_1H_2 interval resulting in definite bundle branch block (BBB) pattern or QRS axis of more than 15 degrees in frontal plane (RRP Ab) or H V prolongation (RRP HV) was taken as the RRP of the HPS

The foregoing definitions of refractory periods apply to conduction along the normal pathways at a given basis cycle length in the absence of antegrade functional bypass tracts

Results

Table I lists the essential clinical data for the 14 patients All patients were in sinus rhythm and had constant P R interval Eight of 14 patients had a normal QRS complex and six out of 14 patients had an abnormal QRS on standard electrocardiogram The mean age of the patients was 51 years

Data on refractory periods for individual patients are listed in Table II and mean values are listed in Table III Table IV lists conduction data for all patients Statistical significance was determined using refractory period data at all cycle lengths Cumulative data were similar to those obtained by comparing refractory period data at the longest cycle length alone

The results on heart rate A V nodal conduction time and refractoriness of atrium and A V node (Table III) were similar to our previously published data[1] No significant change occurred in the effective refractory periods of the atrium and A V node over a 30 minute period Only the FRP of the A V node was significantly decreased ($p < 0.05$) For the purpose of this report only the data on refractory periods and conduction times (H V interval) of the HPS will be presented in detail

His Purkinje conduction His Purkinje conduction time (H V interval) was within the range of normal values in all but two patients (Nos 8 and 11) during control studies *H V intervals remained constant during incremental pacing in all patients After 30 minutes* H V intervals during sinus rhythm and atrial pacing were identical to those of control in all patients

Relative refractory period of HPS

Control data The RRP Ab could be determined in 11 patients and RRP HV in 14 patients

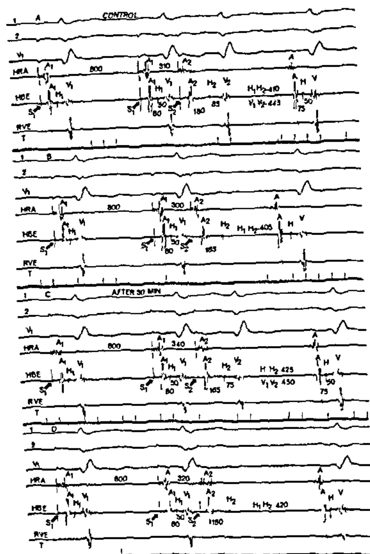


Fig 3 Patient No 10 Effective Refractory Period of HPS The basic paced atrial cycle length is 800 msec in all panels During control at an A A interval of 310 msec *(panel A)* A conducts to the ventricles with an H H interval of 410 msec and an H V interval of 85 msec On decreasing the A A interval to 300 msec *(panel B)* A blocks within the HPS at an H H interval of 405 msec Note that H is not followed by ventricular electrogram (V) This H H interval of 405 msec defines the ERP of HPS for the control period During the repeat study at an A A interval of 340 msec *(panel C)* the A conducts to the ventricles with an H H interval of 425 msec and a longer H V interval compared to basic drive beats As the A A interval is decreased to 320 msec *(panel D)* A blocks within the HPS at an H H interval of 4 0 msec (ERP of HPS) Note an increase of 15 msec in ERP of HPS

during control studies In two patients the RRP HV was encountered before the RRP Ab In three patients RRP Ab was reached before RRP HV while in six others RRP Ab and RRP HV occurred at the same H H_2 intervals In three patients (Nos 2 8 and 12) only the RRP HV could be determined The RRP of HPS decreased as the paced atrial cycle length was decreased

30 minute data The above mentioned relationships between onset of RRP Ab and RRP HV and cycle length dependent changes in refractoriness persisted during repeat studies Average changes in RRP Ab and RRP HV were insignificant ($p > 0.1$) after 30 minutes (Table III Fig 1) Compared to control the RRP HV increased in two patients (Nos 1 and 6) decreased in four patients (Nos 3 5 8 and 9) and was variably altered in one (No 7) depending on the basic

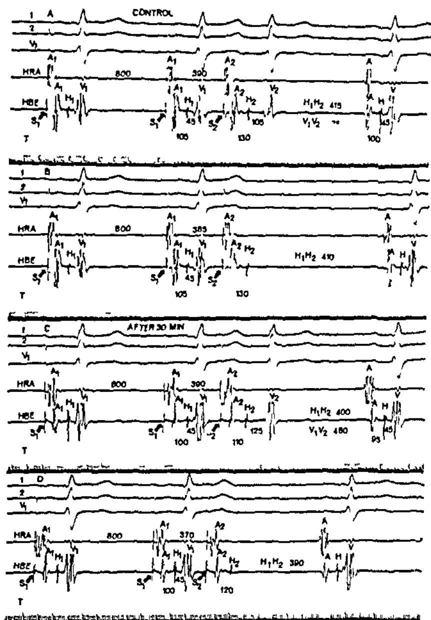


Fig 4 Patient No 1 Effective Refractory Period of HPS The basic atrial cycle length is 800 msec in all panels During the control period at an A A_2 interval of 385 msec *(panel B)* A_2 blocks within the HPS at an H H interval of 410 msec (ERP of HPS) After 30 minutes at a coupling interval of 370 msec *(panel D)* A_2 blocks within the HPS at an H H interval of 390 msec (ERP of HPS) Note a decrease of 20 msec in ERP of HPS

cycle length In seven patients no change from control values occurred in RRP HV Changes in RRP Ab were similar to changes in RRP HV During both control and repeated studies, three out of 14 patients (Nos 3 11 and 14) repeatedly demonstrated varying H_2V_2 intervals within a narrow range of comparable H_1H_2 intervals (Fig 2) In the remaining patients for any given H_1H_2 interval the resulting H V intervals were generally the same as in control (i e within 5 msec)

Effective refractory period of HPS

Control data The ERP of HPS decreased as the paced atrial cycle length was decreased The Mean ERP of HPS for control was 403 ± 38 msec

30 minute data The relationship between cycle length and ERP persisted during repeat studies The mean value for the ERP of HPS after 30 minutes was 401 ± 30 msec which represented a statistically insignificant change ($p > 0\,5$) However a maximum increase of 25 msec and a maximum decrease of 20 msec from control values were seen in individual patients (Figs 3 and 4) Compared to control the ERP of HPS increased in four patients decreased in two patients and was variably altered in four patients depending upon the atrial cycle length at which

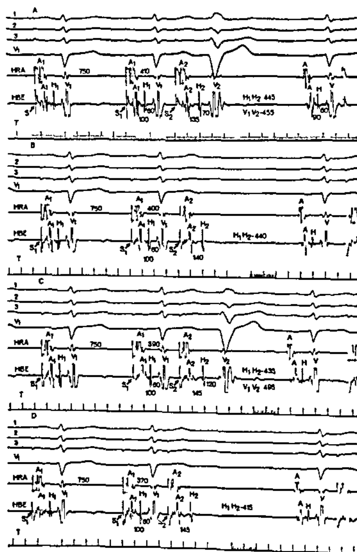


Fig 5 Patient No 11 Type II gap in A V conduction—30 minute study The basic cycle length is constant and measures 750 msec in all panels At an A A interval of 410 msec *(panel A)* A conducts with an H H interval of 445 msec and an H V interval of 70 msec On decreasing the A A interval to 400 msec *(panel B)* A blocks within the HPS at an H H interval of 440 msec *In panel C* at a shorter H H *interval of* 435 msec A V conduction is resumed with a longer H V interval (Type II gap) A V conduction continues to occur on further decreasing of the A A intervals to 370 msec A blocks within the HPS again at an H H interval of 415 msec *(panel D)* The zones of no A V conduction are 5 and 20 msec in duration

testing was done In four other patients the ERP was identical to control values at all paced cycle lengths Changes in ERP of HPS occurred in patients with or without gap phenomena in A V conduction *(see below)*

Functional refractory period data

Control data The FRP of HPS exceeded the FRP of A V node in all patients and at all cycle lengths tested A direct relationship existed between cycle length and FRP of HPS The mean FRP of HPS during control was 432 ± 36 msec

30 minute data During repeat studies cycle length dependent changes in the FRP of HPS persisted A statistically insignificant ($p > 0.5$) increase occurred in FRP of HPS after 30 minutes (432 ± 32 vs 434 ± 37 msec) (Table III) Compared to control the FRP increased in six patients decreased in three patients and was variably altered in two patients depending on the

paced cycle length In three other patients, the FRP remained unchanged from control values

Gap phenomena in A V conduction

Control data A Type I gap in A V conduction was seen in five patients *(Nos 3 8, 10 11, and 12)* and a Type II gap in four patients (Nos 3, 8, 11, and 14) *Three of five patients exhibited both a* Type I and Type II gap in A V conduction (Nos *3, 8 and 11)*

30 minute data In two patients (Nos 3 and 11) a Type I gap could not be demonstrated during repeat studies However, in patient No 3 absence of a *Type I gap occurred only at the shorter cycle* length In patient No 12 a Type I gap was only demonstrated during the 30 minute study Patient No 3 also failed to demonstrate a Type II gap during repeat studies During both control and repeat studies, Type II gaps were generally of short duration (range 5 to 50 msec) and often multiple (Fig 5), while Type I gap zones were single and of long duration No consistent relation was present between the changes in ERP of HPS and the presence or absence of a Type II gap in A V conduction

Blood pressure The blood pressure was not significantly altered in any patient The mean systolic blood pressure was 128 mm Hg for control period and 131 mm Hg after 30 minutes

Discussion

The results of this study confirm previous observations regarding stability of heart rate A V nodal conduction time *and refractoriness of the* atrium and A V node over a 30 minute period[1] *Additionally the results of the present study* suggest that on the average and over a similar *time period the ERP of the HPS remains* unchanged However changes of the magnitude *of 5 to 25 msec in either direction from control* values commonly occur Knowledge concerning behavior of the HPS over *time is important in* assessing cardiovascular drugs which act primarily *on the distal part of the* A V conduction system (e g , procainamide, quinidine etc) Since refractory periods *were measured at comparable cycle* lengths and identical H_1H intervals the frequently observed but insignificant changes may represent physiological variations in the refractoriness of HPS itself Alternative possibilities include changes in autonomic balance and *gap phenomena in A V conduction*

There are conflicting reports regarding the *vagal effects on electrophysiological* properties of ventricular specialized conducting system[illegible] There is some evidence which suggests that the vagus nerve may influence the electrophysiological properties of HPS[7 11] Adrenergic stimulation and administration of catecholamines tend to shorten refractoriness within the HPS[1 13] The net result of interplay between the parasympathetic and sympathetic systems could cause an increase or decrease in refractoriness of HPS Since control heart rates and A H intervals were not significantly altered over time (Table IV) it can be surmised that small changes in refractoriness were not due to any detectable alterations in autonomic balance

The small changes observed in ERP of HPS were not limited to patients with gap phenomena in A V conduction Since Type II gap zones tend to be multiple and zones of no A V conduction short in duration the possibility cannot be entirely ruled out that some changes in ERP were due to gap phenomena Interestingly in three out of four patients in whom the ERP did not change at all, a *Type II gap* phenomenon was not present As previously noted the presence of a *Type II gap in A V conduction* places limitations on the conventional definition of the ERP of HPS[1]

When normal conduction merges into delayed *conduction and when the* RRP merges into the ERP refractoriness of the HPS may not behave *predictably and result in small changes in* refractoriness Delayed conduction and nonhomogeneous *refractoriness are probably* responsible for the conduction of premature beats of identical *coupling intervals with* varying degrees of aberration and different H V intervals

The incidence of block within the HPS during premature atrial stimulation was approximately *10 per cent* (22 out of 254 patients) in the present study It is recognized that this incidence could have been higher had refractory period determinations been performed at longer sinus cycle lengths Interestingly greater than 50 per cent of patients demonstrating block within the HPS had normal QRS complexes

The results of the present study as well as our previous publication on time dependent changes

provide baseline data for future investigations of cardiovascular drugs

Summary

Temporal effects on refractoriness within the His Purkinje system (HPS) were studied in 14 patients in whom effective refractory period (ERP) of HPS could be determined using His bundle electrograms incremental atrial pacing and atrial extrastimulus method His Purkinje conduction times (H V interval) and relative (R) effective (E) and functional (F) refractory periods (RP) of HPS were measured during the control period and repeat measurements were made after a 30 minute interval H V intervals were unchanged from control in all patients Although changes of the magnitude of 5 to 25 msec in either direction from control values commonly occurred on the average no statistically significant changes were seen in RRP ERP or FRP of HPS The results of the present study confirm the stability of refractoriness of HPS over a 30 minute period and provide baseline data for future investigations of cardiovascular drugs which act primarily on the distal part of the A V conduction system

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Hypertrophic cardiomyopathy in the aged

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Hypertrophic cardiomyopathy is a not uncommon disease which has been well characterized since the early reports presenting a composite picture of the disease by Brachfeld and Gorlin,[1] Braunwald and associates, and others.[3] The obstructive variant, also called idiopathic hypertrophic subaortic stenosis, is associated with characteristic clinical findings,[1] including a systolic ejection murmur, unusually brisk carotid pulses bifid apical impulses increase in the intensity of the murmur with Valsalva maneuver, and often associated mitral insufficiency Symptoms and signs include syncope heart failure arrhythmias and angina Left ventricular hypertrophy is often present on the electrocardiogram and chest x ray When any one or more of these abnormalities occurs in a young healthy adult detailed investigation is likely to be carried out and a diagnosis established The echocardiogram has contributed enormously to the non invasive diagnosis of this condition especially in its non obstructive variety (asymmetric septal hypertrophy)

Previous studies have indicated that the disease predominates in the young or middle aged population although instances of hypertrophic cardiomyopathy in older patients have been noted in these studies[6-10] In the past 28 months 23 new cases of hypertrophic cardiomyopathy have been detected at the Cardiac Graphics Laboratory of the Downstate Medical Center Twenty of the patients were over the age of 50 years and form the subject of this report Fifteen of these patients were over the age of 60 years In the majority the correct diagnosis was not made clinically either because it was not considered in these elderly patients or because some of the usual characteristic features were masked or attributed to other conditions more common in this age group Cardiac catheterization is often avoided in the elderly if a clear therapeutic decision is not apparent

The twofold purpose of this paper is (1) to emphasize the occurrence of hypertrophic cardiomyopathy in the older patient in whom the diagnosis is more likely to be missed and (2) to emphasize the apparent compatibility of this disease with long life which in part, conflicts with current thinking on the natural history of the disease

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Received for publication Sept 7 1977
Accepted for publication Nov 7 1977

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Materials and methods

Clinical echocardiograms were performed on a Smith Kline Echocardiograph Model 20A using a Honeywell 1856 ultraviolet recorder and a 2 25 MHz, ½ inch diameter transducer Phonocardiograms and carotid pulse recordings were performed on a Honeywell recorder using two microphones simultaneously each recording in 50 to 120 Hz and 100 to 500 Hz bands or on a Schwarzer six channel direct writing polygraph

Echocardiograms from many of these elderly patients were difficult technically because of overlying lung tissue damping the high frequency sound Nevertheless great care was taken to delineate as well as possible both right and left margins of the interventricular septum in order to define thickness carefully at the level of the mitral valve and posterior wall Echoes from the septal leaflet of the tricuspid valve were carefully differentiated from the right (anterior) margin of the septum

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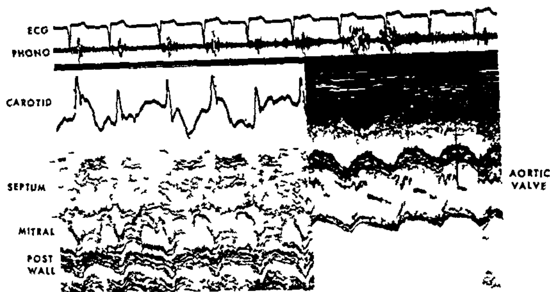


Fig 1 Hypertrophic obstructive cardiomyopathy in a 61 year old woman (H M) with a history of rheumatic fever in childhood and a clinical diagnosis of mitral insufficiency The right side of the septum in this portion of the recording is obscured There is a SAM narrow transverse LV diameter notched aortic valve and spike and-dome carotid pulse

Patient selection Of about 2 000 subjects studied twenty patients over the age of 50 had hypertrophic cardiomyopathy Seventeen of these met the criteria for hypertrophic obstructive cardiomyopathy (e g Fig 1) These required criteria included (a) septal hypertrophy (greater than 1 2 cm thickness) out of proportion to posterior wall thickness (septum/posterior wall thickness ratio 1 4 or greater) (b) systolic anterior motion (SAM) of the anterior mitral leaflet present either at rest or after amyl nitrate inhalation The SAM in all cases was discrete and abrupt It did not appear to be related to underlying papillary muscle motion [1] Additional criteria not sufficient in themselves for diagnosis were (c) anterior displacement and slowing of the early diastolic closing motion of the anterior mitral leaflet in diastole (d) decrease in transverse left ventricular diameter at the level of the mitral valve (usually producing a characteristic "busy" appearance of the recording) and (e) notching of the aortic valves [2] In each case there was no stenosis of the aortic valve

Characteristic pulse abnormalities (Fig 1) were a rapid rate of carotid upstroke with spike and dome configuration [1] Prolonged ejection time index and decreased systolic time intervals were taken as indices of outflow tract obstruction [2] but not differential for valvular vs subvalvular location The presence of pulse abnormalities was considered confirmatory but not diagnostic and the absence of pulse abnormalities did not exclude the diagnosis

In three cases the diagnosis of hypertrophic cardiomyopathy without outflow tract obstruction was based on disproportionate septal hypertrophy (criterion a as above) in the absence of other clinical or echocardiographic explanations for a thickened septum

Results

Patient profile (Tables I and II) The oldest patient in this series was 76 Fifteen of the 20 in the group were 60 years of age or older Fifteen were women The most common presenting complaints (Table I) were syncope or dizziness in nine signs of heart failure in five and chest pain in four In two cases the cardiac lesion was discovered and diagnosed incidental to other unrelated events

Table I Hypertrophic cardiomyopathy in the aged Clinical characteristics

Patient	Age	Sex	Duration of presenting Symptoms	Complaint	Associated findings CHF	Pain	Murmur	HBP	Arrhythmia	Positive family history	Referring diagnoses
D A	65	M	4 yr	HBP dyspnea	+	–	+	+	–	–	HBP CAD ? valve disease
E B	68	F	10+yr	Syncope	++	–	–	+	–	–	HBP CAD ? valve disease
S B	65	F	6 yr	Syncope	++	+	+	++	–	–	MI AS ? HOCM
A B	50	F	3 days	Dyspnea	+	–	+	++	–	–	MI AS
N B	57	F	7 yr	Syncope	+	+	–	–	+	+	Angina ? HOCM
F C	73	F	0	Syncope	–	–	–	–	–	–	AS ? HOCM
E G	58	F	8 yr	Dyspnea	+	+	+	–	+	+	CAD
B J	75	F	4 yr	Pain	–	+++	–	+	–	–	CAD
G L	67	F	60 days	Syncope	+	–	–	–	+	–	AS MI
H M	62	F	4 yr	Dyspnea	+	–	–	+	+	+	MI
A M	63	M	7 days	Pain	–	+	+	+	–	–	AS CAD
M M	76	M	1 yr	Syncope	–	–	–	–	–	–	CAD ? HOCM
J P	75	F	2 yr	Dizziness	+	–	–	+	±	–	AS ?MI ?HOCM
P P	64	M	1 yr	Dizziness	–	–	–	–	–	–	HOCM
E S	73	F	5+yr	Pain	±	+	–	–	–	–	AS MI
R W	68	F	9 yr	Pain	+	+	+	–	–	–	AS CAD
A Wl	61	F	0	None	–	–	+	+	–	–	MI
A Wn	58	F	6 yr	None	+	±	–	+	–	–	CAD
R F	57	F	0 5 yr	CVA	–	–	–	–	–	–	CAD
K M	65	F	41 yr	Dyspnea	+	+	+	+	+	+	AS

Abbreviations HBP = hypertension CHF = congestive heart failure CVA = cerebrovascular accident CAD = coronary artery disease MI = mitral insufficiency AS = aortic stenosis HOCM = hypertrophic obstructive cardiomyopathy Symptoms graded on scale + to +++

The correct diagnosis was suspected in only four cases but was not made definitively by the referring or consulting physician (usually a cardiology Attending or Fellow) Valvular heart disease, either aortic stenosis or mitral insufficiency, or both was considered in 11 hypertensive and/or atherosclerotic heart disease in nine, in one patient both valvular and atherosclerotic heart disease were the prime diagnostic considerations

The duration of symptoms prior to diagnosis averaged 5 5 years, excluding two patients who had no symptoms, and three who had symptoms for less than 1 week *before admission* Seven patients were aware of a heart murmur for at least several years previously, but had not undergone diagnostic study

Palpable carotid pulse abnormalities were present in only five cases all of whom had evidence of outflow tract obstruction on echocardiogram

Carotid pulse tracings (Table III) A spike and dome configuration was recorded in 10 of 18 subjects, and the corrected ejection time index[11] was increased by more than 2 standard deviations from the normal in nine of 17 subjects The systolic time interval (ratio of pre ejection period to ejection time PEP/ET)[12] was less than 0 25 in six of 15 subjects

Echocardiogram (Table III) The average septal thickness was 2 2 cm with a septum/posterior wall ratio of 2 2 in 17 cases A systolic anterior motion (SAM) was recorded at rest, or with amyl nitrate inhalation in 17 cases although in most cases *it was qualitatively not severe* Six patients had increased right ventricular anterior wall thickness, ranging from 4 to 11 mm An incidental finding was a small echo free space posteriorly in eight patients

Cardiac catheterization was performed in seven cases (Table III) Care was taken to avoid catheter entrapment during pressure recordings and

Table II. Hypertrophic cardiomyopathy in the aged Objective clinical data

	Physical findings						Laboratory findings			
Patient	Quick pulse	Ejection murmur	Pan systolic murmur	S_4-S	Blood pressure	Congestive heart failure	Cardiomegaly	ECG	Chest x ray	Cardiac catheterization
D A	+	+	−	+	160/90		+	LVH	LVH	
E B		+	+	+	160/80		+	LVH	Dilated Ao	LV 155/22 C I 3 1 OTG 0 0 with exercise septal bulge in systole
S B		+	−	−	130/80		+	LVH		
A. B		+	+	−	140/90	+	+	LVH	LVH dilated Ao	LV 2[illegible]0/20 C I 2[illegible] OTG 90 2+ aortic insufficiency
N B		−	−	−	130/86		−	RBBB	Nl	LV 130/8 C I 4 2 OTG 26 40 with isoproterenol
F C	±	+	−	−	200/110		+	LVH	Ca mitral annulus Ca cor artery	
E G		+	−	−	130/90		+	LVH LAH	Nl	
B J		−	−	−	150/110		−	RBBB	Nl	LV 160/5 normal EDV obliterated cavity at end systole moderate CAD
G L.		+	+	−	140/70		+	LVH	EH	
H M		+	+	+	120/ 0		+	LVH	EH	LV 165/7 C I 2 6 OTG 35 3+ mitral insufficiency
A M	+	+	−	−	130/90		+	LVH	EH	LV 165/16 C I 3 3 OTG 35 70 with amyl nitrate
M M	+	+	−	+	130/90		+	LVH ASMI PVC	LVH dilated Ao	
J P	+	+	−	+	170/90		+	LVH	LVH	
P P		+	−	−	120/80		+	LVH	LVH	
E S.		+	+	−	130/80	+	+	LVH	LVH pleural effusion	
R W		−	+	+	140/80	+	+	ASMI	Nl	
A. Wl		+	+	−	125/80		−	ST T change	LVH dilated Ao	
A. Wn		+	−	−	200/90		+	Vent Tachycardia	Nl	
R. F		−	+	−	130/80		−	LVH	Nl	
K M		+	−	+	165/55		+	LVH RBBB	EH	LV 200/32 C I 2 6 OTG 0 normal EDV 2+ aortic insufficiency calcified coronary artery

Abbreviations LVH = left ventricular hypertrophy LAH = l ft atrial hypert ophy ASMI = anteroseptal myocardial infarction RBBB = right bundle branch block Ao = orta EH = card megaly LV = l ft entri lar systoli /end-diastol c pressures (mm. Hg) C.I = cardiac inde (L./min / M) OTG = left ventricular o tfl w tract gradie t (mm Hg) nl = normal.

Table III Hypertrophic cardiomyopathy in the aged Graphic data

Patient	Carotid pulse			Phonocardiogram			Echocardiogram							
	Spike and dome	Corrected ejection time (sec)	PEP/ET	Systolic ejection murmur	Pansystolic murmur	S_3 or S	Septum (cm)	Post wall (cm)	S/PW	EDD (cm)	ESD (cm)	SAM	Septal motion	Amyl nitrate effect
D A	–	41	32	+	–	+	2 0	0 9	2 2	3 9	2 5	1+	1+	+
E B	+	43	26	+	+	–	2 4	1 3	1 9	3 6	1 9	2+	2+	ND
S B	–	42	19	+	±	+	1 8	8	2 1	3 9	3 3	0	1+	+
A B	+	44	33	+	–	+	2 0	1 0	2 0	4 2	3 2	4+	1+	ND
N B	+	46	21	–	+	–	2 1	1 1	1 9	4 6	2 8	1+	0	+
F C	–	39		+ +	±	–	2 3	–	–	1 7	1 5	2+	0	+
E G	–	39	37	+ +	–	–	1 6	0 9	1 8	4 0	2 3	2+	1+	+
B J	–			–	–	–	1 8	1 0	1 8	3 5	1 9	0	2+	ND
G L	+	48	19	+ +	+ +	+	2 4	–	–	–	–	2+	3+	+
H M	+	47	34	+ +	–	+	3 3	1 1	3 0	2 9	–	3+	2+	ND
A M							1 9	0 9	2 2	3 9	–	3+	0	+
M M	+	44	28	+ +	+	+	3 3	0 8	4 1	4 4	–	2+	0	ND
J P	+	34	29	+ +	–	–	2 4	0 9	2 7	4 6	–	2+	1+	0
P P	+	48	28	+ +	–	+	2 0	1 0	2 0	4 7	2 7	2+	3+	0
E S	+	49	13	+ +	–	+	2 1	–	–	1 9	–	3+	0	0
R W	+	45	14	+ +	–	+	2 2	1 2	1 8	3 0	–	3+	0	0
A Wl	–	46	15	+	–	+	2 4	1 1	2 2	3 1	1 8	2+	+	0
A Wn	–	41	27	+	–	+	1 9	1 0	1 9	5 0	3 5	0	2+	0
R F							2 1	0 9	2 2	4 5	3 3	4+	0	0
K M	–	40		+	+ +	+	2 0	0 9	2 1	3 9	2 0	0	4+	ND

pullback recording An intraventricular gradient was found at rest in four cases all of whom had evidence of obstruction on the resting echocardiogram In one case there was marked obliteration of the left ventricular cavity at end systole without distortion of the chamber configuration In one case the end systole appearance of the left ventricular cavity had a "bent banana' shape related to septal hypertrophy

Illustrative cases

Case 1 (B J Fig 2) A 75 year old female had severe classical angina pectoris and hypertension for several years without evidence of infarction Physical examination was entirely normal except for a blood pressure of 160/110 before treatment ECG showed right bundle branch block, and heart size and shape were normal on chest x ray At cardiac catheterization there was mild diffuse narrowing of the coronary arteries with no obstruction greater than 50 per cent of the arterial diameter Left ventriculography demonstrated a normal chamber in end diastole and a marked obliteration of the left ventricular cavity at end systole (Fig 1) No outflow tract gradient was present at rest, and in this case isoproterenol stimulation was not performed

Echocardiogram showed marked asymmetrical hypertrophy of the interventricular septum a small left ventricular cavity, and increased thickness of the anterior right ventricular free wall were seen No SAM was demonstrable at rest or after amyl nitrate and the anterior mitral leaflet morphology was normal The patient improved after more intensive treatment with propranolol

Comment This patient had no clinical stigmata of hypertrophic cardiomyopathy except for severe angina The correct diagnosis was made at ventriculography and confirmed by subsequent echocardiography

Case 2 (F C) A 73 year old female was admitted for trauma associated with her first episode of syncope She was otherwise well except for rheumatoid arthritis Carotid pulses were somewhat brisk The apex impulse was tapping, 2 cm left of mid clavicular line and a Grade III+ systolic ejection murmur was heard in the third intercostal space 3 cm to the left of the sternum Electrocardiogram showed mild left

ventricular hypertrophy with small q waves in Leads 1 and aV_L Echocardiogram showed a thick septum SAM small left ventricular cavity abnormal anterior mitral leaflet in diastole and a calcified mitral annulus Fluoroscopy confirmed the calcification of the mitral annulus and showed extensive calcification of the coronary arteries as well Treatment with propranolol 160 mg /day reduced the intensity of the murmur and diminished the SAM on echocardiogram

Comment In the absence of echocardiography the murmur might well have been attributed exclusively to the calcified mitral annulus or to valvular aortic stenosis

Case 3 (N B) A 57 year old female complained of chest pain syncope and palpitation for seven years Her mother was said to have had an enlarged heart for at least 30 years Her first two syncopal episodes were associated with seizures and pulmonary congestion was diagnosed clinically 2 years previously Physical examination showed slightly distended neck veins without right ventricular heave A right bundle branch block was present on electrocardiogram X ray of the chest was normal Carotid pulse studies showed a spike dome configuration the PEP/ET was 0 21 and the ejection time index was increased A regurgitant systolic murmur was recorded at apex and lower left sternal border Echocardiogram showed a thickened septum (2 1 cm) with a septum/posterior wall ratio of 1 9 A small SAM was present which was increased by amyl nitrate The mitral EF slope was 45 At cardiac catheterization a 25 mm Hg subvalvular outflow tract gradient was found The ventriculogram showed a markedly reduced end systolic volume the coronary arteries were normal

Comment In this case the symptoms were sufficiently vague and atypical that cardiac neurosis was suspected initially

Case 4 (R W) A 68 year old female was told of a murmur many years previously She had angina for 9 years and signs of congestive heart failure for 3 years She was thought to be hypothyroid She was admitted for acute chest pain and found to have an apex impulse in fifth interspace near the anterior axillary line There was a Grade III pansystolic murmur at apex an S gallop and basilar râles Electrocardiogram suggested an anterior subendocardial infarction without left ventricular hypertrophy X ray showed the heart to be at normal size Pulse and heart sound recording showed a spike and dome configuration with prolonged ejection time PEP/ET was 0 14 and a regurgitant murmur was seen Echocardiography showed a thickened septum (2 2 cm) and a septum/posterior wall ratio of 1 8 with prominent SAM narrowing the outflow tract diameter in systole to 3 mm

Fig 2 Hypertrophic non-obstructive cardiomyopathy in a 6-year-old woman with mild hypertension and s vere angina pectoris Angiogram shows marked reduction of end systolic cavity similar to the echocardiogram which showed a septum 1 8 cm thick

Comment In this patient there was electrocardiographic evidence of associated coronary heart disease The murmur and heart failure would have been attributed to papillary muscle dysfunction and myocardial infarction exclusively whereas the hypertrophic obstruction may have played a significant role

Case 5 (E B) A 68-year old female had a long history of heart disease and dyspnea with

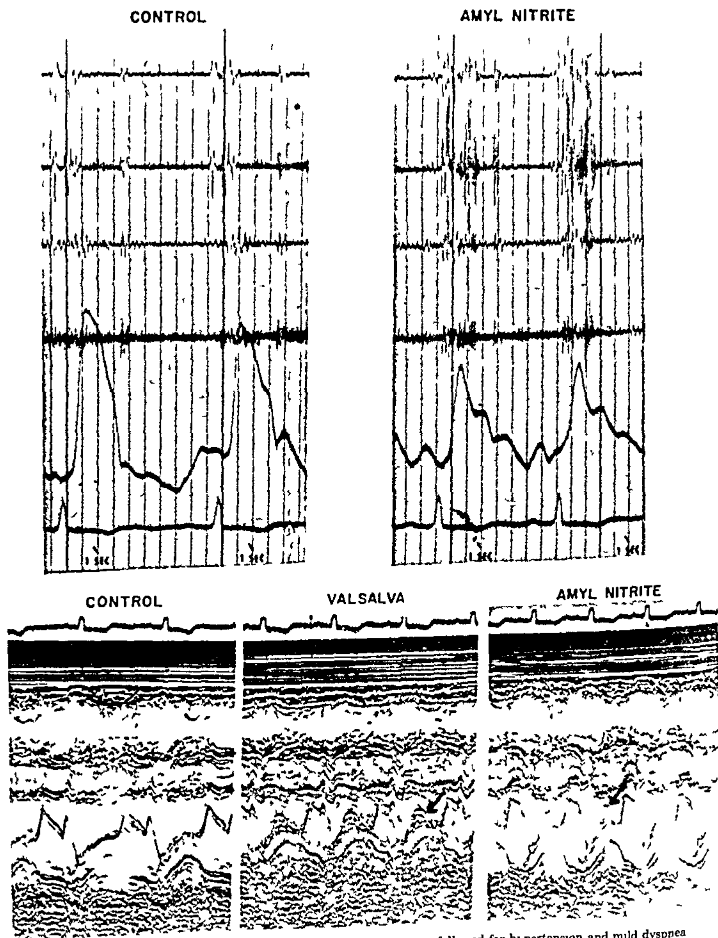


Fig 3 Hypertrophic cardiomyopathy in a 65 year old man being followed for hypertension and mild dyspnea The septum is thick but obstruction is not present at rest With Valsalva maneuver and amyl nitrate inhalation a murmur carotid pulse abnormality and SAM appear

rdiomegaly known for 6 years She was being eated for mild hypertension when she was lmitted for syncope associated with a respira ory infection BP was 160/80 An S gallop was resent A regurgitant murmur was present at the pex and a systolic ejection type murmur was eard along the sternal border which radiated to he neck ECG and x ray indicated left ventric ilar hypertrophy Carotid pulse showed a spike lome pattern with normal ejection time index ind PEP/ET and 0 26 Phonocardiogram con irmed the ejection and regurgitant murmurs The echocardiogram revealed a thickened septum (2 4 cm) with septum/posterior wall ratio of 1 9 2+ SAM with 4 mm systolic outflow tract diameter and the mitral leaflet was displaced anteriorly The aortic valve was noted to be notched late in systole Propranolol 2 mg admin istered intravenously during the study decreased the SAM within five minutes

Case 6 (D A Fig 3) This 65 year old man was told of a leaky valve at age 17 but knew no more of heart disease till 5 years prior to study (age 60) when he noted dyspnea on walking rapidly Cardiomegaly was noted and he was being treated for hypertension His mother died in her thirties during the 1918 influenza epidemic a son died suddenly during a soccer match without known prior heart disease Blood pressure was 160/90 There was an apical systolic ejection murmur increasing during Valsalva maneuver and an S_4 was present The pulses were normal and the ECG showed LVH Echocardiogram and phonocardiogram showed development of a mur mur and SAM during amyl nitrate inhalation There was moderate asymmetric septal hypertro phy

Comment This patient has apparently mild disease clinically The findings could have been dismissed as compatible with hypertension The son who died during exertion was presumably severely affected

Discussion

Hypertrophic cardiomyopathy is easily diag nosed in young or middle aged patients when there are characteristic clinical findings[1] consist ing of dyspnea or signs of congestive heart failure chest pain syncope or palpitations in association with the findings of a brisk carotid upstroke and a systolic murmur heard best along the left sternal border which is poorly transmitted to the neck The picture is complete with an ECG meeting the criteria of left ventricular hypertrophy and a chest x ray revealing a small ascending aorta and left ventricular predominance Mitral insuffi ciency is frequently present occasionally domi nating the clinical picture

In the aged our clinical study of hypertrophic obstructive cardiomyopathy shows that the diag nosis was frequently missed similar to the experi ence of Hamby and Antablian[11] and Whiting and colleagues[10] The symptoms and signs are frequently misinterpreted as manifestations of more common diseases such as coronary artery disease or hypertensive heart disease Mild hyper tension common in this age group is frequently considered the basis of the cardiomegaly Syncope or dizziness a common presenting sign in this series as in that of Whiting and associates[0] may be ascribed to cerebrovascular insufficiency or heart block The brisk carotid pulse may be ascribed to rigidity of the arterial walls or conversely it may be sluggish due to associated intrinsic atherosclerotic and thrombotic disease (one patient in this series had total obstruction of a carotid artery and underwent endarterectomy) The ascending aorta may be dilated rather than small leading one to ascribe the systolic murmur to aortic stenosis The associated mitral insuffi ciency was often explained as papillary muscle dysfunction or as in one patient in our series to a calcified mitral annulus

Carotid pulse tracings and heart sound record ings offer important clues to the proper diagnosis but the echocardiogram provides the most accurate specific diagnostic support short of cardiac catheterization The characteristic echo cardiographic features include a thickened sep tum out of proportion to the thickness of the posterior left ventricular wall an anterior mitral valve leaflet echo showing anterior posterior an anterior systolic motion often abutting the septum and a slow early diastolic closing motion Septal motion is often diminished but may be normal The left ventricular valve cavity is small and the record appears busy The aortic valve leaflets appear thin and open widely but may show a notch of midsystolic closure

The extensive use of the echocardiogram in a large medical teaching service contributed to the increasing frequency of diagnosis in a group of

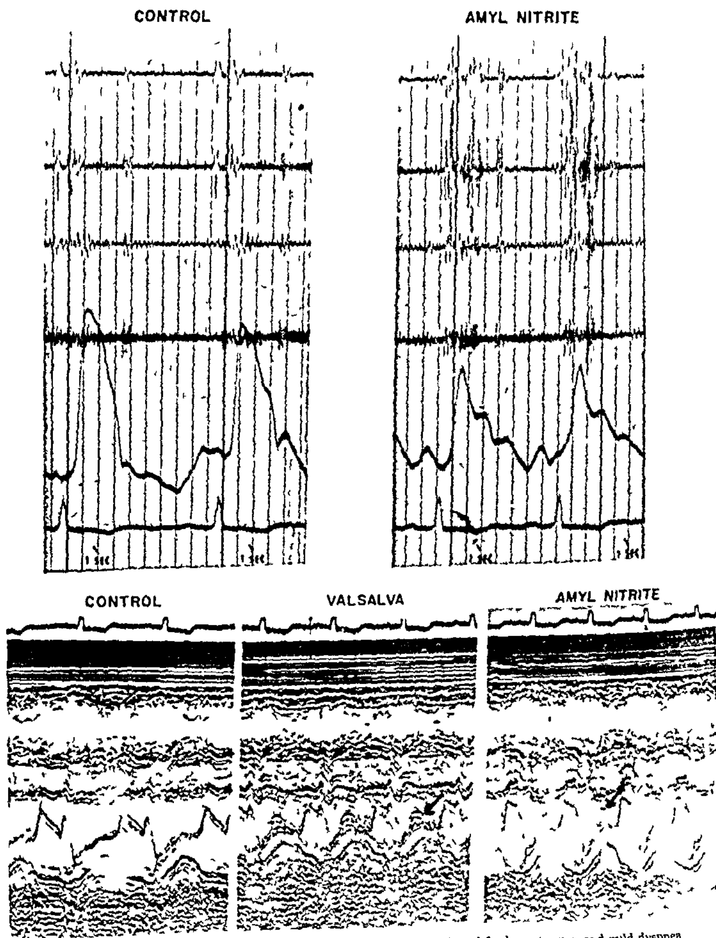


Fig 3 Hypertrophic cardiomyopathy in a 65 year old man being followed for hypertension and mild dyspnea The septum is thick but obstruction is not present at rest With Valsalva maneuver and amyl nitrate inhalation a murmur carotid pulse abnormality and SAM appear

nt the result not the cause of prolonged)struction[19] and could possibly be progressive in laracter The mechanism of progressive obstruc on may become clearer now that longitudinal udies by echocardiography are possible

A corollary of the thesis of progressive develop ient of the lesion is that the clinical course is low In several recent studies a gradual progres ion of symptoms is described for many patients egardless of the clinical classification of the patients when first studied Hardarson and olleagues[7] postulates a long phase of asymptom atic disease until about age 30 after which symp toms may supervene with progressive clinical deterioration Sudden death can occur at any time in this course however even in asymptom atic subjects responding well to medical or surgical therapy In the 49 patients followed for an average of 7 5 years by Hanania and asso ciates[17] 66 per cent survived 20 years from the onset of the first symptoms These data support the concept of Hardarson and co workers[7] on the prolonged course of the disease

To confound the description of the natural history and prognosis further Hanania and colleagues[7] found that more cases improved with time than deteriorated treatment with propra nolol did not account for this result Adelman and co workers and Powell and colleagues[20] also noted significant improvement in many patients of their respective series attributing the change to medical therapy with beta adrenergic blocking drugs but without a true control series for comparison The present series thus extends the *potential survival curve even further than that suggested by Hardarson Hanania and their asso* ciates

Summary

Although usually considered a disease of young or middle aged adults hypertrophic cardiomyop athy is not infrequently seen in older patients as well Twenty of 23 cases of hypertrophic cardio myopathy seen in the past $2^{1}/_{2}$ years at our institution have been in patients whose average age was 65 years and who ranged up to 76 years Sixteen of these had evidence of an obstructive component at cardiac catheterization or echocar diography Symptoms and signs were similar to those described for the younger patients in the literature but were often attributed to other causes including valvular aortic stenosis ar teriosclerotic or hypertensive heart disease or cerebrovascular disease Left ventricular hyper trophy was more consistently present on ECG than on x ray

The not infrequent occurrence of hypertrophic cardiomyopathy in older patients predominantly females indicates that the natural history of this disease includes a group who suffer few or no symptoms until late in life Clinical management of younger patients with this diagnosis should be considered in light of this more favorable possible course

The excellent technical assistance of Mrs Henrietta Stokes and Miss Shirley Staiano and secretarial assistance of Mrs Yetta Israelite is gratefully acknowledged

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patients who otherwise would have remained misdiagnosed had cardiac catheterization been required. It is to be expected that the increasing utilization of the echocardiogram will be associated with fewer missed diagnoses of hypertrophic cardiomyopathy in the elderly.

Hypertrophic cardiomyopathy is more common in older people than was previously thought. In earlier series of hypertrophic cardiomyopathy, aged patients were rare and most patients were young or middle aged adults or children. In the series of 119 patients followed by Hardarson and colleagues[7] only one was over 60 years of age and Adelman and associates[8] reported on 60 patients the oldest of whom was 55. In the large early series of 126 patients analyzed by Frank and Braunwald[11] only two were over 60. None of the 18 patients reported by Parker[9] was over 45. Recently, however, Whiting and colleagues[10] reported 14 cases over the age of 60, and Hamby and Aintablian[14] found nine cases of hypertrophic cardiomyopathy in patients over 70. In our present series of 23 cases of hypertrophic cardiomyopathy of all ages seen in the past 3 years, 20 were over the age of 50 years.

The recognition of hypertrophic cardiomyopathy in patients in the seventh and eighth decades of life, some of whom who are even then minimally symptomatic, extends our understanding of the natural history of the disease from that portrayed in previous studies. The patients in this series suggest that the lesion of hypertrophic cardiomyopathy is compatible with a long life and that selected patients may remain asymptomatic to a late age. The explanation for this more benign prognosis in selected patients is not clear. Two possible explanations suggest themselves: one is that this group of patients had a relatively mild degree of obstruction and thus survived to old age; the other is that the obstructive process is not present in early years but develops and progresses in the course of aging.

The possibility of our series representing a milder form of the obstructive lesion is suggested by the small resting gradients at cardiac catheterization and normal cardiac indices among the seven subjects who underwent cardiac catheterization. Also the echocardiogram did not suggest high grade obstruction[11]—i.e., the outflow tract was not completely obliterated for long periods of systole in most patients. Previous studies do not, however, suggest a milder obstructive lesion in the elderly. Whiting and associates[10] found more severe gradients at catheterization among the older patients, as compared to the younger group. Pomerance and Davies[16] found severe hypertrophy at necropsy in the older patients with average heart weight of 560 grams, even though in some cases of their series the lesion was an incidental finding and was not symptomatic or diagnosed during life.

There is, however, difficulty in defining clinical severity of this disease, especially when sudden death may occur at any stage of disease unheralded by any symptoms. There is disagreement among investigators as to the prognostic usefulness of clinical or hemodynamic parameters. Hanania and colleagues[17] found that clinical prognosis related only to the age of onset of symptoms. One agreed upon datum is the poorer prognosis of the familial form of the disease compared to the sporadic form.[7,17] Only four subjects in the present series had a history suggestive of familial disease, but this datum is not reliable since in a number of our cases the family history was not well known to the patient.

The present study with its predominance (N per cent) of female patients suggests also that males may have a severer form of the disease. In the series of Frank and Braunwald[11] there was an equal sex incidence in younger patients, but in the older patients, females predominated. Hamby and Aintablian[1] also found seven females out of nine aged patients with hypertrophic cardiomyopathy. In the series of necropsy cases studied by Pomerance and Davies[16] the sex incidence was equal, but females averaged 76 years of age compared to 66 for males. Whiting and coworkers[10] found 10 of 14 elderly patients to be females. One could thus infer that women have a better chance of living longer with the disease.

The second possible explanation for the prolonged survival is that in this disease, albeit often a familial one, the obstructive process is not present in early years, but develops and progresses with age. This contention is supported by the work of Williams and colleagues,[7] who documented the development of the obstructive component over 4 years in a 15 year old girl. Even the disordered myocardial architecture previously thought to be a feature of the congenital myopathic character of the disease may repre

Effects of rapid digitalization on total and regional myocardial performance in patients with coronary artery disease*

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The hemodynamic effects of acute digitalization have been studied extensively in experimental animals,[5] in normal human subjects,[6] and in patients with congestive heart failure.[8] Similar studies were also carried out in patients with coronary artery disease (CAD) who were not in overt left ventricular (LV) failure.[7] In contrast, little is known about the influence of rapid digitalization on LV volumes and ejection fraction in man. Furthermore, although many patients with CAD develop LV wall motion abnormalities, there is very little pertinent information concerning the possible effects of digitalis therapy on these areas of disordered contractility.

Since it has been shown that digitalis increases myocardial oxygen consumption when given to experimental animals with nonfailing hearts, it has been postulated that the increased myocardial oxygen demand could lead to greater myocardial ischemia in CAD patients without heart failure.[15] Furthermore, it has been demonstrated that positive inotropic stimulation of surviving myocardium in the experimental animals may accentuate the extent of paradoxical systolic motion. The area of paradoxical motion may act as a slack, elastic element in series with the contractile portions of the remaining left ventricle.[17] Because of this slack area, increased velocity of contraction would be required to generate tension during isovolumic systole, thereby increasing cardiac work—an effect which could further increase myocardial oxygen consumption.[8, 9]

It is therefore apparent that subjects with CAD and LV asynergy but no heart failure may represent a category of patients who would not benefit from digitalis therapy and could actually be harmed. This study was undertaken to determine hemodynamic, volumetric, and regional wall motion changes that occur in patients with chronic CAD after rapid digitalization, and to establish whether digitalis could exert a salutary effect on areas of disordered LV contractility.

Materials and methods

Twenty-one consecutive patients with suspected CAD were selected for this study. All gave informed consent and underwent routine diagnostic cardiac catheterization studies, which in our laboratory include complete left and right heart hemodynamic evaluation, cardiac output determination with the green dye indicator dilution technique, selective left ventriculography, and coronary arteriography. All patients were in normal sinus rhythm. None had systemic hypertension, congestive heart failure, or significant valvular or congenital lesions.

Some of the patients received various cardiovascular medications in the past, but in each

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Received for publication Aug. 8, 1977.

Accepted for publication Sept. 30, 1977.

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*Presented in part at the 26th Annual Scientific Session of the American College of Cardiology, Las Vegas, Nevada, March, 1977.

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skinesis were encountered An asynergic seg ent was considered to have improved following e administration of ouabain when it showed a 10 per cent increase[33] and became worse when exhibited a ≥ 10 per cent decrease in per cent iortening

Cardiac output (CO) arterial-venous differ ice and pressure data were collected prior to ich ventriculogram Cardiac output was deter ined by the Lyons green dye indicator dilution omputer Aortic (AP) and pulmonary artery PAP) systolic diastolic and mean right and left entricular systolic and end diastolic mean right trial (RAP) and mean pulmonary capillary vedge (PCWP) pressures were measured in each ase with Statham model P23Db strain gauges ind recorded with an Electronics for Medicine DR 12 Simultrace recorder The maximum rate of rise of LV pressure (dP/dt) was obtained with a fluid filled system and a Model RC 1 differen circuit which has a time constant of 0 5 msec and an output that is linearly proportional to the input frequency within ± 5 per cent Heart rate was monitored throughout the study In addition systemic vascular resistance (SVR = [mean AP – mean RAP]/CO) pulmonary vascu lar resistance (PVR = [mean PAP – mean PCWP]/CO) LV stroke work index (LVSWI = SVI × [LV systolic mean – LV_{ED}] × 0 0136)[3] and mean velocity of circumferential fiber short ening (V_{CF} = d_{ED} – d_{ES}/d_{ED} × ejection time where d_{ED} and d_{ES} are left ventricular minor axes in end diastole and end systole)[16] were calculated for each patient The normal range for V_{CF} in our laboratory is 1 07 ± 0 24 circ /sec

All coronary cineangiograms were of high tech nical quality Significant CAD was considered to be present only when there was at least a 75 per cent occlusion of at least one of the three coro nary arteries and when this observation was confirmed by two independent observers When ever coronary collaterals were present the origin and the extent of these collaterals were recorded in detail

Data were analyzed with Student s t test The t test for non paired variables was used when comparing intergroup differences while data comparing pre and post ouabain values within a single group were analyzed with the t test for paired variables All statistical calculations were performed on the Sigma 7 computer at the University of California Irvine

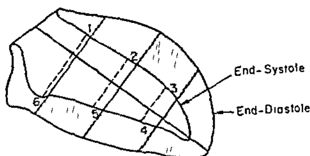


Fig 1 Normal left ventricular silhouette in end systole and end-diastole End systolic and end-diastolic images were fitted with a longitudinal axis which was quadrisected by six hemiaxes (*solid hemiaxes* end-diastole *dashed hemiaxes* end systole)

Results

Of the 21 patients studied (20 males and one female) all had the chest pain syndrome Seven patients had no CAD detected on coronary angio grams and served as normal (control) subjects (Group I) Fourteen patients had extensive coro nary disease (Group II) The mean age of patients in Group I was 46 ± 5 years and in Group II 53 ± 7 years (P not significant) Age related changes in ouabain pharmacology[34] therefore had minimal (if any) effect on the results of this study

The complete hemodynamic and volumetric data for Groups I and II before and after ouabain administration are given in Tables I and II All pre ouabain parameters in both groups were within the normal limits After ouabain adminis tration both groups exhibited virtually identical directional responses in all measured parameters Specifically the LV end diastolic pressure re mained essentially unchanged in both groups Similarly ouabain failed to appreciably alter the LV filling pressure systemic and pulmonary vascular resistance or the heart rate Cardiac index and LV stroke work index increased slightly after ouabain administration in normals and in patients with CAD but this increase was not statistically significant In contrast the systolic and mean aortic pressure and the indices of contractility (V_{CF} and dP/dt) rose significantly after ouabain infusion in both groups

Volumetric analysis revealed that LV end diastolic volume *does not change* significantly after ouabain administration There was a signif icant decrease in the end systolic volume follow ing ouabain in both groups however with

instance all drugs were discontinued at least 5 days prior to the study without any clinical evidence of deterioration of cardiac function, or increase in chest pain Only one patient was on a prior chronic digitalis therapy, but this drug was considered to be unnecessary, and was stopped one month before the study without any adverse effects The only drug continued up to the day of the study was sublingual nitroglycerin None of the patients had to take nitroglycerin for at least 12 hours prior to cardiac catheterization

After the completion of the first ventriculogram 0 007 mg /Kg of ouabain was infused intravenously over a five minute period The infusion mode of administration was deliberately selected in order to produce less variability in the pharmacokinetic constants, [9] and to minimize the effects of ouabain on systemic and coronary vascular resistance which have been shown to increase significantly if this drug is given as a bolus [1] The total amount of administered ouabain (based on the 0 007 mg /Kg dosage) ranged from 0 50 to 0 75 mg which is commonly accepted to represent the total digitalizing dose for an average adult [2]

Following the first ventriculogram (and after the infusion of ouabain) coronary arteriography was performed Sixty minutes after the first ventriculography (and 20 minutes after coronary angiography) the second left ventriculogram was done The time span of 60 minutes was selected to assure the peak effect of ouabain and to eliminate the pharmacological effects of the contrast medium on myocardial contractility [3, 24] Furthermore 20 minutes were allowed to elapse after the coronary cineangiography in order to avoid the possible effects of transient reactive hyperemia on myocardial contractility [25, 6]

The reproducibility of the angiographically determined volumes and ejection fraction derived from the two left ventriculograms done during the same catheterization and at a comparable hemodynamic state have been examined previously in our laboratory In consensus with the data reported by other investigators [7] no significant difference was found between volumes and ejection fraction determined from the two sequential studies Furthermore McAnulty and associates [8] have shown that sequential ventriculograms without any pharmacological interventions reproduce areas of LV asynergy that are constant in site and magnitude, and can therefore be used to study the effects of medical a... surgical treatment on left ventricular wall motion abnormalities

Both selective left ventriculograms we... obtained with a No 8 Cordis pigtail catheter which was positioned in the left ventricle Forty five to 50 ml of 76 per cent meglumine sodium diatrizoate (Renografin 76) were injected over a 3 second interval Left ventriculograms in 3... degree right anterior oblique position were recorded at 64 frames per second on 35 mm Ilford Cinegram F film with Philips 9 inch image intensifier Only the first four beats after complete opacification were analyzed by two independent observers If an infrequent premature ventricular contraction was encountered, at least two successive normal sinus beats (following the premature beat) had to occur before a frame was selected for analysis

A modification [9] of the area-length method of Dodge[30] was used in the analysis of all LV volumes End diastolic volume index (EDVI), end systolic volume index (ESVI), stroke volume index (SVI) and ejection fraction (EF = SVI/EDVI) were calculated for each patient

Each ventriculogram was also interpreted qualitatively for vigor and uniformity of contraction at all points along the ventricular outline A quantitative analysis was performed by combining previously described approaches[31, 32] a... using internal thoracic structures (spine, rib margins or a diaphragm) as fixed reference systems End systolic (ES) and end diastolic (ED) images were fitted with a longitudinal axis (obtained by dividing the images with a connecting line between the bisected aortic valve and the ventricular apex) and six hemiaxes (perpendicular to the longitudinal axis which was divided into four equal segments) (Fig 1) The longitudinal axis and each hemiaxis were then measured and normalized as per cent decrease (or increase) in length from the end diastolic dimension

$$\% \text{ shortening} = \frac{\text{ED axis} - \text{ES axis}}{\text{ED axis}} \times 100$$

A hypokinetic zone was defined to occur when < 25 per cent hemiaxis shortening was observed in the initial ventriculogram [33] According to the classification of Herman and associates[34] hypokinesis represented the mildest form of asynergy, followed by increasingly more pronounced LV wall motion abnormalities when akinesis and

kinesis were encountered An asynergic seg at was considered to have improved following administration of ouabain when it showed a 10 per cent increase and became worse when exhibited a ≥ 10 per cent decrease in per cent ortening

Cardiac output (CO) arterial–venous differ ce and pressure data were collected prior to ch ventriculogram Cardiac output was deter ined by the Lyons green dye indicator-dilution mputer Aortic (AP) and pulmonary artery AP) systolic diastolic and mean right and left ntricular systolic and end diastolic mean right rial (RAP) and mean pulmonary capillary edge (PCWP) pressures were measured in each se with Statham model P23Db strain gauges id recorded with an Electronics for Medicine R 12 Simultrace recorder The maximum rate rise of LV pressure (dP/dt) was obtained with a iid filled system and a Model RC 1 differen ating circuit which has a time constant of 0 5 sec and an output that is linearly proportional the input frequency within ± 5 per cent Heart ite was monitored throughout the study In ddition systemic vascular resistance (SVR = nean AP – mean RAP]/CO) pulmonary vascu r resistance (PVR = [mean PAP – mean CWP]/CO) LV stroke work index (LVSWI = VI × [LV systolic mean – LV_{ED}] × 0 0136)[9] nd mean velocity of circumferential fiber short ning ($V_{CF} = d_{ED} - d_{ES}/d_{ED}$ × ejection time here d_{ED} and d_{ES} are left ventricular minor axes end diastole and end systole)[10] were calculated or each patient The normal range for V_{CF} in our boratory is 1 07 ± 0 24 circ /sec

All coronary cineangiograms were of high tech ical quality Significant CAD was considered to e present only when there was at least a 75 per ent occlusion of at least one of the three coro ary arteries and when this observation was onfirmed by two independent observers When ver coronary collaterals were present the origin nd the extent of these collaterals were recorded detail

Data were analyzed with Student s t test The test for non paired variables was used when omparing intergroup differences while data omparing pre and post ouabain values within a ingle group were analyzed with the t test for aired variables All statistical calculations were erformed on the Sigma 7 computer at the Jniversity of California Irvine

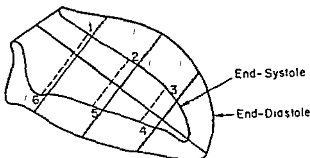


Fig 1 Normal left ventricular silhouette in end-systole and end-diastole End systolic and end-diastolic images were fitted with a longitudinal axis which was quadrisected by six hemiaxes (*solid hemiaxes* end-diastole *dashed hemiaxes* end systole)

Results

Of the 21 patients studied (20 males and one female) all had the chest pain syndrome Seven patients had no CAD detected on coronary angio grams and served as normal (control) subjects (Group I) Fourteen patients had extensive coro nary disease (Group II) The mean age of patients in Group I was 46 ± 5 years and in Group II 53 ± 7 years (P not significant) Age related changes in ouabain pharmacology[15] therefore had minimal (if any) effect on the results of this study

The complete hemodynamic and volumetric data for Groups I and II before and after ouabain administration are given in Tables I and II All pre ouabain parameters in both groups were within the normal limits After ouabain adminis tration both groups exhibited virtually identical directional responses in all measured parameters Specifically the LV end diastolic pressure re mained essentially unchanged in both groups Similarly ouabain failed to appreciably alter the LV filling pressure systemic and pulmonary vascular resistance or the heart rate Cardiac index and LV stroke work index increased slightly after ouabain administration in normals and in patients with CAD but this increase was not statistically significant In contrast the systolic and mean aortic pressure and the indices of contractility (V_{CF} and dP/dt) rose significantly after ouabain infusion in both groups

Volumetric analysis revealed that LV end diastolic volume *does not change* significantly after ouabain administration There was a signif icant decrease in the end systolic volume follow ing ouabain in both groups however with

Table I Hemodynamic and volumetric data before and after ouabain administration—Group I (normals)

Parameter	Before ouabain (mean ± 1 SD)	After ouabain (mean ± 1 SD)	P
LVEDP (mm Hg)	8 ± 3	9 ± 2	N S
RVEDP (mm Hg)	3 ± 1	4 ± 1	N S
Syst AP (mm Hg)	113 ± 15	130 ± 26	<0 05
Diast AP (mm Hg)	70 ± 6	74 ± 9	N S
Mean AP (mm Hg)	91 ± 11	99 ± 13	<0 05
Mean PAP (mm Hg)	12 ± 3	14 ± 3	<0 05
Mean RAP (mm Hg)	3 ± 1	4 ± 1	N S
Mean PCWP (mm Hg)	5 ± 2	6 ± 2	N S
SVR (dynes sec-cm ⁵)	1 220 ± 238	1 129 ± 213	N S
PVR (dynes sec-cm ⁵)	105 ± 24	93 ± 37	N S
dP/dt (mm Hg/sec)	1,285 ± 391	1 487 ± 466	<0 05
(A V)O_2(vol %)	4 0 ± 1 3	3 5 ± 1 3	N S
CI (L /min /M)	3 1 ± 0 6	3 6 ± 0 4	N S
LVSWI (Gm m /M²/ beat)	47 ± 11	60 ± 16	N S
V_{cf} (circ /sec)	0 99 ± 0 19	1 19 ± 0 15	<0 001
HR at ventriculogram (beats/min)	76 ± 9	73 ± 12	N S
EDVI (ml /M)	72 ± 23	74 ± 23	N S
FSVI (ml /M²)	21 ± 8	15 ± 5	<0 01
SVI (ml /M²)	50 ± 13	58 ± 20	N S
EF (%)	70 ± 6	79 ± 4	<0 01

Abbreviations AP = arterial pressure (A V)O = arterial venous difference CI = cardiac index dP/dt = rate of rise of ventricular pressure EF = ejection fraction EDVI = end-diastolic volume index ESVI = end-systolic volume index HR = heart rate LVEDP = left ventricular end-diastolic pressure LVSWI = left ventricular stroke work index NS = not significant PAP = pulmonary arterial pressure PCWP = pulmonary capillary wedge pressure PVR = pulmonary vascular resistance RAP = right atrial pressure RVEDP = right ventricular end-diastolic pressure SD = standard deviation SVI = stroke volume index SVR = systemic vascular resistance V_{cf} = mean velocity of circumferential fiber shortening

resulting marked increase in the LV ejection fraction (P < 0 01)

In order to determine if Group I (normals) and Group II (patients with coronary disease) represented markedly different patient populations, the pre and post ouabain intergroup values were compared No statistically significant differences were found to exist between Groups I and II for either hemodynamic or volumetric parameters

None of the patients in Group I but eight patients in Group II had regional disorders of LV contractility, delineated by 23 abnormal hemiaxes of shortening In each case, the area of asynergy was supplied by a critically narrowed coronary artery After ouabain administration 15

Table II Hemodynamic and volumetric data before and after ouabain administration—Group II (patients with coronary artery disease)

Parameter	Before ouabain (mean ± 1 SD)	After ouabain (mean ± 1 SD)	P
LVEDP* (mm Hg)	9 ± 5	9 ± 4	N S
RVEDP (mm Hg)	4 ± 2	4 ± 2	N S
Syst AP (mm Hg)	129 ± 21	137 ± 2[illegible]	<0 0[illegible]
Diast AP (mm Hg)	72 ± 9	73 ± 1[illegible]	N S
Mean AP (mm Hg)	95 ± 13	100 ± 17	<0 0[illegible]
Mean PAP (mm Hg)	13 ± 3	13 ± 3	N S
Mean RAP (mm Hg)	3 ± 2	4 ± 2	N S
Mean PCWP (mm Hg)	6 ± 4	6 ± 3	N S
SVR (dynes sec-cm ⁵)	1 149 ± 276	1 146 ± 234	N S
PVR (dynes sec-cm ⁵)	91 ± 30	92 ± 33	N S
dP/dt (mm Hg/sec)	1 677 ± 576	2 078 ± 571	<0 0[illegible]
(A V)O_2 (vol %)	4 3 ± 1 2	4 4 ± 1 1	N S
CI (L /min /M²)	3 4 ± 0 8	3 6 ± 0 [illegible]	N S
LVSWI (Gm m /M²/ beat)	46 ± 14	50 ± 18	N S
V_{cf} (circ /sec)	0 85 ± 0 24	0 98 ± 0 30	<0 0[illegible]
HR at ventriculogram (beats/min)	78 ± 12	74 ± 10	N S
EDVI (ml /M²)	72 ± 14	70 ± 14	N S
ESVI (ml /M²)	25 ± 7	22 ± 7	<0 01
SVI (ml /M²)	46 ± 13	49 ± 13	N S
FF (%)	64 ± 10	70 ± 9	<0 01

See Table I for abbreviations

out of 23 asynergic segments (65 per cent) improved seven remained unchanged, and one worsened (Fig 2) In general only hypokinetic segments managed to return to normal contractility while akinetic and dyskinetic segments remained in the asynergy zone despite the improvement in their contraction A typical study is illustrated in Fig 3

Ten patients out of 14 in Group II were found to have angiographically demonstrable collateral circulation Among them, three patients with extensive collaterals had no LV asynergy Alternately collaterals were present in all but one patient with the LV asynergy The single patient with the abnormal LV wall motion and no collateral circulation showed the least improvement in the regional LV contractility upon ouabain administration The other three patients however, not only had no collaterals but also had no LV asynergy

At the completion of each ventriculographic or coronary angiographic analysis the interobserver differences were examined There was only a

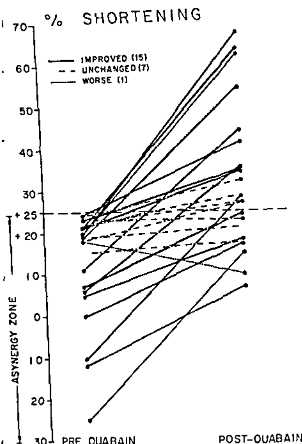


Fig 2 Response to ouabain by 23 abnormal hemiaxes of shortening Fifteen asynergic left ventricular segments improved seven remained unchanged and one became worse

negligible variance in the values obtained by the two observers

Discussion

The hemodynamic data for Group I (normal) patients in the present study confirm earlier observations that digitalis enhances the contractile force (characterized by dP/dt V_{CF} ect) of the normal heart Various investigators[3] have described significant increases in LV dP/dt after intravenous administration of cardiac glycosides to human subjects with normal or nonfailing hearts Peak active force and the maximal rate of force development were increased by an average of 21 per cent when digitalis was given to normal experimental animals Sonnenblick and associates found marked increases in the velocity of myocardial shortening after infusion of ouabain to six patients with normal cardiac status

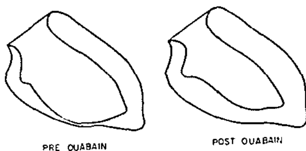


Fig 3 A representative ventriculographic study in a patient with left ventricular asynergy The pre-ouabain ventriculogram shows hypokinesis of the inferior wall (segments 4 5 and 6) Marked improvement in the contraction of the inferior wall is noted after ouabain administration.

In contrast cardiac output exhibited only an insignificant rise in Group I patients This finding is consistent with the accumulated evidence that cardiac output and the contractile state of the normal myocardium cannot be related to one another in a simple manner and that augmentation of the latter does not necessarily elevate cardiac output [4]

The slight increase in the LV stroke work index in the normal subjects is apparently due to the systemic vasoconstriction after ouabain administration and the accompanying rise in the LV systolic pressure The presence of vasoconstriction and rise in the systolic pressure is also reflected by the significant increase in the mean aortic pressure—a phenomenon that has been previously observed after acute digitalization [51] The concomitant increase in the systemic vascular resistance was not observed however probably because it was maintained at the pre ouabain levels by the simultaneous increase in the cardiac output

LV end diastolic volume and pressure remained unchanged in Group I after ouabain administration The effects of digitalis on LV volumes and ejection fraction in a normal man have not been previously studied Some investigators have postulated that normal LV end diastolic volume decreases after acute digitalization presumably because LV end diastolic pressure fell in their experiments while the aortic pressure was held constant Yet the LV end diastolic pressure more accurately reflects the status of LV compliance rather than end diastolic volume so that in some patients with chronic heart disease volumes three to four times normal may occur with diastolic pressures that are normal [53] Covell and co workers [5] found only a slight decrease of LV end

diastolic volume and pressure in normal experimental animals after digitalis administration if the aortic pressure was maintained at a constant level In an ultrasound study, Mahler and associates[54] demonstrated no appreciable change in the LV end diastolic diameter after daily intramuscular injections of digoxin, even though the LV systolic pressure increased by 10 mm Hg from the average control value

LV end systolic volume decreased, and LV ejection fraction significantly increased in Group I patients after ouabain administration While no other angiographic studies are available for comparison, two ultrasound investigations[54, 55] have yielded comparable data Both studies[54, 55] have shown that in normal subjects the mean end systolic dimension decreased, and ejection fraction increased[55] after digitalis was administered

The baseline hemodynamic and volumetric values for patients with CAD (Group II) corresponded closely to their normal (Group I) counterparts and exhibited almost identical changes after ouabain administration It is, therefore, clear that digitalis produces fundamentally similar responses when given to normal patients or to patients with chronic CAD and nonfailing hearts There was a uniform and significant increase in all measured indices of LV contractility dP/dt velocity of circumferential fiber shortening, and LV ejection fraction after ouabain administration to Group II patients Similar enhancement of the LV inotropic state had been observed by other investigators[12, 56, 57] after digitalization of patients with chronic CAD In contrast Cohn and associates[58] have reported acute deterioration of cardiac function in a small number of patients with CAD after rapid digitalization All of their patients were also in congestive heart filure however and therefore probably represent a different spectrum of subjects than do the patients in this study

In a recent report De Mots and co workers[5] have noted a decrease in the LV end diastolic pressure and volume after ouabain administration to patients with chronic CAD who were thought not to be in congestive heart failure These observations are contrary to the findings of our study in which LV end diastolic volume and pressure remained essentially unchanged after ouabain infusion Two possibilities could account for this discrepancy (1) Patients in the study of De Mots and colleagues had borderline elevation of LV end diastolic pressure (11 5 ± 1 4 mm Hg and marked elevation of LV end diastolic volume (100 ± 17 ml /M ^{2}) in comparison to the normal LV end diastolic value of 70 ± 20 ml /M ^{2} established by Dodge and Baxley[59] It is therefore possible that these patients were in the incipient congestive heart failure which was not clinically apparent, and responded to ouabain with a decrease in the LV end diastolic volume and pressure (2) In our study, the mean arterial blood pressure rose after ouabain administration while the LV end diastolic pressure remained unchanged In contrast De Mots and colleagues describe not only a decrease in the LV end diastolic pressure but also a drop in the mean arterial pressure after ouabain administration Since it has been demonstrated that decreases in preload and afterload diminish LV end diastolic dimensions[60] the lower post ouabain LV end diastolic volumes in the study of De Mots and colleagues may be secondary to these hemodynamic alterations

While the results of this study clearly demonstrate that the total LV performance improves when cardiac glycosides are administered to patients with chronic CAD, it was of critical importance to determine if the regional disorders of ventricular contractility also benefit by digitalis therapy In eight patients from Group II who had LV asynergy 15 out of 23 abnormally contracting segments improved (65 per cent) seven remained unchanged and only one deteriorated after digitalization This marked decrease in the regional abnormalities of LV contraction could be considered a relatively unexpected finding Namely all of the patients with LV asynergy had normal LV volumes and were not in congestive heart failure Therefore, their myocardial oxygen consumption should increase after ouabain administration[16, 61] resulting in an additional metabolic burden to the already ischemic asynergic zones, hence accentuating the abnormal LV wall motion even further Similar deleterious effects following acute digitalization have been demonstrated in the experimental animals with ischemic myocardial injury but no ventricular enlargement the epicardial mapping technique registered augmentation of myoca damage after infusion of ouabain[4- 63] U natel recent reports[64, 65] question the re of epicardial ST segment mapping in p

the severity of myocardial ischemia and the previous conclusions[6, 63] may no longer be valid or directly applicable to the findings of this study

Three recent studies have investigated the contractile performance of infarcted intermediate ischemic and non ischemic ventricular zones in experimental animals after acute myocardial injury[66-68] Digitalis augmented contratility of the intermediate (border) zones indicating that ischemic myocardium retains the capacity to respond to the positive inotropic stimuli of cardiac glycosides Similar conclusions were reached in a noninvasive study which employed videotracking technique to determine the effect of digitalization on the LV wall motion in patients with a prior myocardial infarction[6] While our report represents the first combined hemodynamic-angiographic investigative effort to determine the response of abnormally contracting LV myocardium to digitalis administration in human subjects it is in agreement with the noninvasive and experimental animal studies which have indicated that LV asynergy improves after digitalization

Numerous mechanisms may be responsible for the improvement of LV asynergy in patients with CAD when treatment with cardiac glycosides is instituted It has been shown that ouabain increases glucose transport to myocardial tissues[7, 1] and that the enhanced sugar uptake may be associated with the increased positive inotropic effect of the drug[1] Yet it is very doubtful that this mechanism is of major importance in improving contraction of ischemic myocardium in order to provide the required adenosine triphosphate for normal muscular contraction from carbohydrate anaerobically at the same rate as during aerobic metabolism the glucose utilization rate must increase approximately nineteen fold

Many investigators have examined the role of endogenous catecholamine release which normally follows the administration of digitalis and how this release modifies the inotropic action of the drug Some[3, 5] conclude that catecholamine stores are not essential for the positive inotropic effect of cardiac glycosides while others claim that the enhanced inotropic action of digitalis is closely linked to the increase in catecholamine concentration in the circulating blood It has been shown that administration of catecholamines (l-epinephrine) can improve LV motion abnormalities in patients with CAD[15] This improvement presumably takes place due to the increased blood flow to marginally ischemic myocardium possibly through collateral channels or through interdigitation of primary vessels originating from the unoccluded coronary artery[79, 80] It is conceivable that a similar mechanism contributed to the improvement of the LV wall motion abnormalities after ouabain administration in our patients with LV asynergy

A great deal of controversy still exists about the effect of collateral circulation on LV asynergy[81, 83] It has been shown that digitalis directly augments the coronary collateral blood flow and decreases the myocardial oxygen consumption whenever it reduces the LV diastolic pressure or increases the m an coronary perfusion gradient[8, 85] Seven of our eight patients with LV asynergy had extensive coronary collaterals and while there was no change in the LV diastolic pressure after the administration of ouabain the diastolic aortic pressure displayed a modest rise therefore causing a slight increase in the coronary perfusion pressure It is unresolved if this phenomenon caused an improvement in LV asynergy—not only because of the minim l rise of the coronary perfusion gradient but also because the angiographic visualization of a collateral vessel gives no information about the blood flow that this vessel can actually carry

Despite the fact that some—or even all of these mechanisms may alter the contractile properties of ischemic myocardium after the administration of cardiac glycosides the primary positive inotropic effect of digitalis on the normal heart is produced by its binding to a site on the cell membrane which in turn results in a series of changes involving the Na K -ATPase and ultimately provides additional calcium to the contractile proteins[85, 8] While considerably attenuated[6] the uptake of digitalis continues into the ischemic border zones of the heart[90] It is very likely that it is this fundamental property of cardiac glycosides which is primarily responsible for the increase in contractility of the ischemic myocardium after digitalization

Summary

In order to evaluate the effects of rapid digitalization on LV volumes ejection fraction and asynergy 21 patients without heart failure were studied with a combination of hemodynamic and

angiographic techniques before and after administration of intravenous ouabain (0 007 mg /Kg) Seven patients had no CAD and served as normal (control) subjects (Group I), while 14 patients had extensive coronary disease (Group II) All pre ouabain parameters were within the normal limits in Group I After ouabain infusion, all indices of LV contractility dP/dt, V_{CF}, and ejection fraction rose significantly in the normal group, while LV filling pressure and end diastolic volume remained unchanged

The baseline hemodynamic and volumetric values for Group II patients corresponded closely to their normal (Group I) counterparts and exhibited similar changes after ouabain administration Eight patients in Group II also had regional disorders of LV contractility, delineated by 23 abnormal hemiaxes of shortening After ouabain, 15 out of 23 asynergic segments (65 per cent) improved seven remained unchanged and one worsened It is therefore concluded that rapid digitalization not only enhances LV performance in normal subjects and in patients with CAD, but can also markedly reduce the extent of LV asynergy

The authors wish to thank Clifford Risk Ph D for statistical analysis of all the data and Mrs Wilma Mottin for her extensive secretarial help in the preparation of this manuscript

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Non invasive assessment of left internal mammary–coronary bypass patency using the external Doppler probe

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The purpose of this paper is to report a new method for the non invasive assessment of left internal mammary-coronary artery bypass patency

Material and method

The study group was comprised of 14 consecutive subjects who underwent left anterior descending coronary artery bypass utilizing the left internal mammary artery All patients had angina pectoris considered refractory to therapy with nitrites propranolol and other medication Twelve of 14 subjects also had saphenous vein bypass procedures for obstructive disease in the balance of the coronary artery system All patients underwent cardiac catheterization 1 to 8 months ($\bar{x} = 4.2$) into the postoperative period The latter study included native coronary arteriography left ventriculography and opacification of saphenous vein and internal mammary artery bypass grafts

Non invasive assessment of internal mammary arterial graft patency was performed within 48 hours of catheterization by means of a commercially available non directional Doppler ultrasonic probe (Model No 803 Parks Electronics Laboratory Beaverton Oreg) The principles of this technique and its application for the study of phasic instantaneous blood flow velocity have been previously described in detail [1] With subjects in the supine position the Doppler probe tip was placed at the second intercostal space at the left and right sternal borders At these respective sites the internal mammary artery

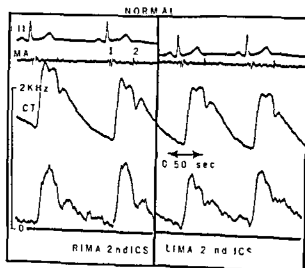


Fig 1 Simultaneously recorded Lead II (LII) of the electrocardiogram mitral area *(MA)* phonocardiogram external carotid artery pulse tracing *(CT)* and blood velocity signals recorded at the second intercostal *spaces (ICS)* Right *(RIMA)* and left *(LIMA)* internal mammary artery blood velocities are characterized by a large systolic wave succeeded by a smaller diastolic fraction

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Supported in p rt by th E Nichols a d Kim S gsw rth M m rial F nds, nd the Inst tute for Cardio ascular Diseases I c
Recei ed for public tion Sept 1 1977
Accepted f r publ tion Sept. 21 19 7

Reprint req ests Alberto Ben humol, M D Good Sam ritan Hospital, P O Box 2989 Phoenix Ari 85006.

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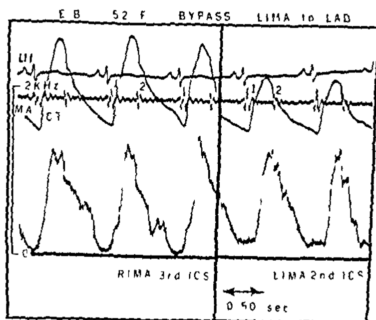


Fig 2 Lead II (LII) of electrocardiogram mitral area *(MA)* phonocardiogram external carotid artery pulse tracing *(CT)* and non invasive Doppler blood velocity signals from the right and left internal mammary arteries of a 52 year old woman with a patent left internal mammary artery graft to the left anterior descending coronary artery Note the high amplitude phasic left internal mammary blood velocity recorded at the second left intercostal space The internal mammary artery graft was angiographically patent

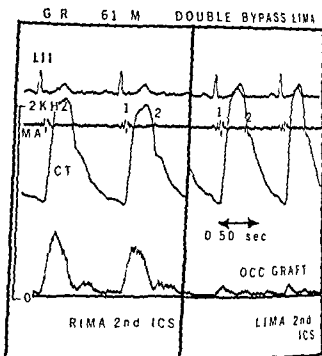


Fig 3 Lead II (LII) of electrocardiogram mitral area *(MA)* phonocardiogram *external carotid arterial pulse tracing (CT)* and internal mammary artery blood velocity in a 61 year old man with an occluded left internal mammary artery bypass to the left anterior descending coronary artery Note the marked reduction of left internal mammary artery *(LIMA)* blood velocity at the second intercostal space

blood velocity profile was detected such ultrasonic signals were characterized by a large systolic wave followed by a smaller diastolic fraction Movement of the probe tip inferiorly along the parasternal border defined the internal mammary artery and its audible blood velocity signals These latter blood velocity waveforms were easily distinguished from those of the intercostal arteries which require angulation of the Doppler probe tip toward the inferior border of the overlying rib for detection

In two cases external Doppler blood velocimetry was performed in the catheterization laboratory during internal mammary graft angiography Fluoroscopic image intensification demonstrated that the Doppler probe tip was directly over the site of internal mammary graft flow

Blood velocity signals Lead II of the electrocardiogram phonocardiograms and external carotid pulse tracings were simultaneously recorded in an Electronics for Medicine DR 8 oscilloscopic-photographic recorder and stored on tape Fig 1 demonstrates characteristic internal mammary artery blood velocity signals from a normal subject

Results

Of 14 patients studied 13 had patent left internal mammary artery grafts demonstrated at cardiac catheterization Twelve of these 13 subjects had normal left internal mammary arterial Doppler blood velocity waveforms (Fig 2) A 61 year old man with aortic-right coronary artery saphenous vein and internal mammary artery-left anterior descending coronary artery bypass grafts was referred for angiography because of recurrent angina pectoris Both grafts were shown to be proximally occluded at the time of cardiac catheterization External Doppler ultrasonic examination indicated a marked attenuation of phasic left internal mammary artery blood velocity signals (Fig 3) A single patient with a patent left internal mammary artery graft was found to have a reduction of peak external Doppler blood velocity Flow in this particular graft was qualitatively designated as sluggish at angiography

Discussion

External Doppler ultrasonography has been applied for the determination of saphenous vein

oronary bypass patency[2] Owing to its relatively uperficial anatomic location the left internal mammary artery is amenable for study with the ungated non directional Doppler ultrasonic probe Significantly no subject with an angiographically patent internal mammary graft had absent blood velocity signals on non invasive study with this technic

Advantages of the method include (1) ease of application (2) non invasive audible features and (3) potential for widespread ambulatory follow up of such patients A larger series of subjects with occlusion of left internal mammary artery grafts at different sites must be systematically studied in order to determine the frequency of false positive and false negative results The unidirectional non invasive Doppler probe applied in this study does not estimate the magnitude of blood flow actually delivered to the myocardium by the internal mammary graft Despite this drawback the method does provide information regarding some characteristics of blood transport within these structures

Summary

Non directional blood velocity of left internal mammary bypass grafts was non invasively studied with the Doppler ultrasonic probe Thirteen of 14 subjects had angiographic evidence of bypass graft patency and their Doppler signals demonstrated high amplitude phasic blood velocities A single patient with proximal left internal mammary arterial graft occlusion manifested marked attenuation of Doppler blood velocity signals It is concluded that this technic offers a potential for ambulatory and in office screening of internal mammary artery bypass graft function

We would like to acknowledge the technical assistance of Carole Crevier Sydney Peebles and Kathleen Tustison

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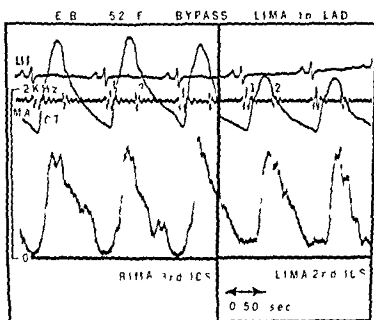


Fig 2 Lead II (LII) of electrocardiogram mitral area (MA) phonocardiogram external carotid artery pulse tracing (CT) and non invasive Doppler blood velocity signals from the right and left internal mammary arteries of a 52 year old woman with a patent left internal mammary artery graft to the left anterior descending coronary artery Note the high amplitude phasic left internal mammary blood velocity recorded at the second left intercostal space The internal mammary artery graft was angiographically patent

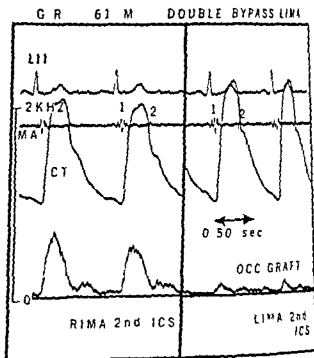


Fig 3 Lead II (LII) of electrocardiogram mitral area (MA) phonocardiogram external carotid arterial pulse tracing (CT) and internal mammary artery blood velocity in a 61 year old man with an occluded left internal mammary artery bypass to the left anterior descending coronary artery Note the marked reduction of left internal mammary artery (LIMA) blood velocity at the second intercostal space

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Discussion

External Doppler ultrasonography has been applied for the determination of saphenous vein

Table I Clinical details and trial data in 20 patients with intractable angina

				Trial data					
				Placebo			*Perhexiline*		
Patient number	*Age & sex*	*Previous therapy*	*Coronary artery disease (% block)*	*Weekly GTN*	*Social home & job activities*	*Total work (kpm)*	*Weekly GTN*	*Social home & job activities*	*Total work (kpm)*
1	46 M	Propranolol	RCA100 LAD 50 C75	13	No change	1823	7	Improved	2430
2	57 M	Propranolol	RCA100 LAD90 C25	20	No change	1343	18	No change	1400
3	57,M	Propranolol	RCA100 LAD90 C25	15	Decreased	2564	15	Improved	3816
4	55 F	Propranolol	RCA50 LAD50	114	No change	610	66	Improved	DNA
5	46 M	Oxprenolol	RCA50 LAD30	35	Decreased	3135	25	No change	1596
6	44,M	Propranolol	RCA75 LAD50 C[illegible]5	DNT	No change	1230	DNT	Improved	4010
7	53 F	Oxprenolol	RCA50 C[illegible]5	5	Improved	1[illegible]09	12	Decreased	630
8	45 M	Atenolol propranolol	RCA75 LAD[illegible]5 C50	4[illegible]	Decreased	[illegible]34	13	Improved	1[illegible]66
9	49 M	Propranolol	RCA100 C50	6	Improved	1836	15	Decreased	612
10	6[illegible] M	Oxprenolol, metoprolol	RCA75 LAD75 C50 LMS[illegible]5	DNT	No change	26[illegible]6	DNT	No change	304[illegible]
11	[illegible]3 F	Propranolol	C50 LAD25	5	Decreased	454	1	Improved	1188
12	53,M	Propranolol	RCA100 C100	8	Decreased	319[illegible]	5	Improved	8840
13	53 M	Oxprenolol	RCA50	DNT	No change	1453	DNT	No change	6240
14	48 M	Oxprenolol	LAD75 C100	8	Decreased	1813	2	Improved	4884
15	46,F	Propranolol oxprenolol	RCA25 LAD50 C25	15	No change	1188	16	Slightly improved	1166
16	[illegible]1 M	Oxprenolol metoprolol	RCA100 C25	37	Decreased	2277	15	Improved	6120
17	38 M	Propranolol	RCA100 LAD75 C25	7	Decreased	4158	2	Improved	5676
18	47 F	Oxprenolol	RCA100 LAD50	DNT	No change	300	2	Improved	1217
19	[illegible]1,M	Oxprenolol	C75 LAD50	DNT	Decreased	1[illegible]30	DNT	Improved	3696
20	49 M	Propranolol	RCA75 LAD50 C50	6	No change	4453	2	Improved	61[illegible]0

Abbreviations GTN = glyceryl trinitrate LMS = left main stem C = circumflex artery DNA = did not attend RCA = right coronary artery LAD = left anterior descending DNT = did not tolerate

completion of the trial A decision was made if there was a definite increase in exercise tolerance and a clear improvement in one of the three following parameters reduction in GTN consumption reduction in anginal crises and improvement in home social or job activities Improvement in any of the three activities was accepted when a patient was able to do more without angina i e dancing brisk walking gardening etc On the other hand deterioration meant that such activities had to be abandoned or curtailed because of angina Each improvement was awarded +1 and each deterioration −1 Student's paired t test was used to assess the statistical significance between placebo and perhexiline data

Results

Eight patients could not complete the trial three had aortocoronary bypass graft surgery two withdrew during the first period (one perhexiline and one placebo) because of an increase in angina one left the area and the two others stopped because of dizziness tremor aches and pains When the code was opened one of these two patients was found to have been taking placebo These eight patients did not differ from the other 20 patients as regards their coronary angiographic findings and GTN consumption Their mean weekly GTN consumption during the two week pre trial period was 25 tablets as compared with a mean of 27 tablets used by those who completed the study Of the remaining 20 patients 14 preferred perhexiline to placebo three (patient numbers 5 7 and 9) preferred placebo and in the three others (patient numbers 2 10 and 15) no decision could be made (*Table I*) Of the 14 patients who benefited from perhexiline 12 improved within the first two weeks of treatment Patient numbers 18 and 19 noticed a marked

Assessment of perhexiline maleate in angiographically proven intractable angina A double-blind trial

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The long term treatment of angina has remained unsatisfactory in spite of various therapeutic advances Numerous reports show that between 20 and 50 per cent of patients with angina do not respond to beta blocking drugs [1-4] Aortocoronary bypass graft surgery is ineffective in about 20 per cent patients[5-8] and the number of patients with intractable angina tends to increase as the time passes after surgery [11]

Perhexiline maleate (Pexid) a new anti anginal drug has been found to be effective in over 70 per cent of patients with angina [11-13] These investigators have suggested that perhexiline is effective in many patients with beta blocker resistant angina [11-14] The purpose of this study was to assess the efficacy of perhexiline in intractable angina

Patients and methods

Twenty eight patients with intractable angina who had not responded to 480 mg or more of propranolol or oxprenolol were invited to participate in this study Coronary angiography showed significant disease (i e at least 50 per cent block in one or more vessels) in all Fourteen patients had three vessel disease, 13 had two vessel blocks and one patient had single vessel disease Their mean age was 51 years (range 38 to 62 years) (Table I)

This was a randomized double blind placebo controlled study and consisted of a two week control period during which beta blocking agents were withdrawn followed by two six week treatment periods In each period patients took one tablet (perhexiline 100 mg or placebo) twice a day Of the first seven patients two had to be withdrawn because of an increased frequency of angina (one on placebo and one on perhexiline) and two others experienced no benefit in either period The single dose policy was therefore changed to a fixed two dose level as the eighth patient was entered in the *trial so* that all patients thereafter had one tablet twice a day for the first two weeks of each period and two tablets twice a day for the remaining four weeks of either period

Each patient attended for an exercise test on a bicycle ergometer (Monark, Sweden) on three occasions before starting the trial at six weeks (the cross over point) and at the completion of the trial at 12 weeks The patients were instructed not to take glyceryl trinitrate *(GTN)* on the test day These patients were severely disabled and we started with low work loads and increased stepwise until angina occurred Heart rate was monitored and recorded through Lead V_5

Patients were seen and examined at two weekly intervals They kept a record of anginal crises (prolonged angina unresponsive to *GTN)* GTN consumption and of any other symptoms Blood was collected for transaminases and a Vickers analysis at each visit

The patient preference for either period was decided by us before the code was broken at the

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0002 8703/78/0396-0350$00 50/0 © 1978 T v Mosby Co

myocardial oxygen extraction[1] Animal experiments have suggested that perhexiline dilates coronary vessels[1] but Pepine and co workers[7] were unable to confirm this in humans Perhexiline like beta blocking drugs but not through beta blockade reduces exercise induced tachycardia and delays angina by a reduction in the rate of rise of heart rate during exercise[1] Our results confirm that perhexiline reduces exercise induced tachycardia (Table II) but this is unlikely to be the sole explanation for its beneficial effects in angina One of our patients (case 17) improved on perhexiline (Table I) but his heart rate was 30 beats per minute faster than on placebo at the points of angina

Eight patients (29 per cent) had to be withdrawn from this trial Three of these had surgery and only two patients taking perhexiline withdrew because of an increase in angina or side effects The incidence of side effects in this study was higher (50%) than reported by other workers but these did not seriously interfere with patients daily activities The rise in serum transaminases was transient as observed in other trials

We conclude that perhexiline is a valuable drug for treating intractable angina when beta blockers are contraindicated or have failed It has a special place in those patients in whom there are no graftable vessels beyond a blocked coronary artery and in whom angina has recurred after surgery Perhexiline is also worth considering when surgical risks are expected to be high

Summary

We report a randomized double blind placebo controlled trial on perhexiline Twenty eight patients with beta blocker resistant intractable angina were included but only 20 of these completed the 12 week period of the trial Perhexiline was effective in 14 patients (70 per cent) as shown by a significant ($P < 0.01$) decrease in glyceryl trinitrate consumption and in anginal crises. Exercise tests on a bicycle ergometer showed a significant ($P < 0.01$) increase in exercise tolerance and a reduction in exercise induced tachycardia Three patients experienced profound relief from angina and declined to have aortocoronary bypass surgery The main side effects were tremor dizziness and nausea but these did not seriously incapacitate the patients

We conclude that perhexiline is a valuable drug for treating intractable angina especially when surgery is not feasible

We thank Drs. E G Wade G Howitt and D J Rowlands for allowing us to study the patients under their care Our thanks are due to Dr H C Masheter of Richardson Merrell Ltd for advice and for the supplies of perhexiline and placebo used in this study

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Table II Clinical and exercise response to perhexiline compared with placebo

	Placebo	Perhexiline	Difference between perhexiline and placebo
Mean resting heart rate	79	80	±1 P = NS
Change in heart rate at comparable loads (mean)	44	27	−17 P < 0 01
Work performance (mean KPM)	1975	3356	+1381 P < 0 01
Weekly GTN consumption (mean)	23	14	−9 P < 0 005*
Weekly anginal crises (mean number)	13	6	−7 P < 0 01

Student s paired t test

reduction in anginal attacks in the third week when the dose of perhexiline had been doubled

GTN consumption and anginal crises Five patients did not tolerate GTN The remaining 15 patients consumed a mean of 23 GTN tablets a week during placebo and 14 tablets (P < 0 005) during the perhexiline period (Table II) The mean number of anginal crises (duration 10 to 12 minutes, unresponsive to GTN) was 13 per week during the placebo period and it dropped significantly (P < 0 01)to 6 per week during the perhexiline period

Exercise performance Exercise data were obtained in 19 patients one patient (Case 4) went on holiday and did not attend for the test Fifteen patients improved their exercise performance (work load × speed × time) during the perhexiline period and they were able to exercise longer and against higher loads until the point of angina The increase in the total work varied from 8 per cent (patient 2) to 329 per cent (patient 13) with a mean of 70 per cent (P < 0 01) (Tables I and II) Four patients (cases 5 7 9 and 15) performed better during the placebo period The resting heart rate was not different during the two periods but the increase in the heart rate at the comparable work load was significantly (P < 0 01) less on perhexiline (27 beats per minute) than on placebo (44 b p m)

Home social and job activities Ten patients showed improvement and two showed deterioration in all the three activities during perhexiline period A paired t test showed a significant (P < 0 05) over all benefit from perhexiline as compared with placebo

Side effects Fourteen patients (50 per cent) had side effects, two during the placebo period Dizziness, tremor aches and pains and nausea occurred frequently but were troublesome in only two patients who withdrew from the trial One of these was on placebo

Eleven patients showed a slight rise in serum transaminases (SGOT in all and SGPT in 2) nine of these were on perhexiline 400 mg a day while two patients were on placebo These last two patients had also a slightly elevated creatine kinase (CPK) level, and the rise in transaminases in these two was probably caused by a myocardial ischemic episode The rise in transaminases was transient and reverted to normal within two weeks in all but two patients There was no rise in serum bilirubin or alkaline phosphatase levels

Discussion

Perhexiline was beneficial in 14 patients with intractable angina as shown by a significant reduction in GTN consumption and in anginal crises an improvement in social or home activities and an increase in exercise tolerance Six of these (patients 1, 2 5, 7, 14 and 17) had triple vessel disease and seven (patients 3 9 10 12 13, 15, and 16) had two vessel disease Their angina had not responded to an adequate trial with beta blocking therapy and aortocoronary bypass surgery was the only treatment with some chance of relieving their symptoms However surgery is not without risk, the mortality rate is higher in patients with multiple vessel disease than in single vessel disease A distinct minority derive no benefit from surgery and have late complications [6 7] It must be pointed out that while surgery relieved angina completely in nine out of 29 patients with intractable angina operated upon in our Unit (unpublished data) perhexiline improved only three patients (20 per cent) (cases 3 4 and 16) to an extent which led to their declining bypass graft surgery In the remaining 11 responding patients the anginal episodes were significantly reduced but not completely relieved

The mode of action of perhexiline is not clear though there is some evidence that it increases

Comparative influence of ouabain norepinephrine and heart rate on myocardial oxygen consumption and inotropic state in dogs

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It is well recognized that tension development in the heart is an important determinant of myocardial oxygen consumption Another major determinant of myocardial oxygen consumption (MVO) is the velocity of myocardial contraction which is an index of the inotropic state of the heart A positive linear relationship between MVO and the maximum contractile element velocity has been demonstrated in the intact canine heart when inotropic state is augmented by norepinephrine or by increasing heart rate However it is not known whether the magnitude of this relationship is the same or different when inotropic state is increased to the same extent by various positive inotropic interventions

Whereas cardiac glycosides and aglycones have been shown to increase the inotropic state of both normal and failing myocardium it has been reported that these agents either decrease increase [5 7] or produce no change in MVO However in many of these studies myocardial tension development was uncontrolled and since tension development is an important determinant of MVO_2 changes of this factor might have obscured a positive relationship between inotropic state and MVO

Coleman[9] demonstrated that when peak developed tension was maintained constant in isometrically contracting cat papillary muscles acetylstrophanthidin increased both the rate of force development and MVO Covell and associates [5] reported similar results for the intact canine heart when there was little change in developed tension Although these studies indicate there is a positive relationship between inotropic state and MVO when inotropic state is augmented by acetylstrophanthidin they do not show whether the magnitude of this relationship is the same as that which exists when inotropic state is augmented by other positive inotropic interventions It was the purpose of the present investigation to directly compare the effects of ouabain and norepinephrine on the relationship between maximum contractile element velocity (i e inotropic state) and myocardial oxygen consumption and further to compare the results produced by these pharmacologic agents with results obtained previously where inotropic state and myocardial oxygen consumption were increased by increasing heart rate In order to avoid problems related to changes in tension development an isovolumic left ventricular preparation in dogs was employed in which peak left ventricular wall stress (stress = tension per unit cross sectional area) was maintained constant in each experimental animal

From th Card ascular Servi e and Labo atori s United States Publi H lth Servic Hosp t L B ltimore Md and the D partm nts of Pediatrics a d Pharm c logy Vand rbilt Uni ers ty School f Medicine Nashvil e Tenn

This ork was supported in part by G nt A-69-5 f the Fede l He lth Programs Service—USPHS a d by PHS G a t HL 1 629

Recei ed f publi ation J ly 1 19 7

A cepted fo publ ation Feb 13, 19 8

Reprint requests R bert C Boerth, M D Di is n of Pediatri Clinical Pharm col gy Dept of Pediatrics, V nd b lt U i ersity School f Med cine Nash ill T nn 3 23

0002-8 03/ 8/0396-0355$00 80/0 © 1978 The C V Mosby Co

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Table I Effects of norepinephrine and ouabain on left ventricular dynamics and myocardial oxygen consumption

	Norepinephrine		*Ouabain*	
	Control	*Drug effect*	*Control*	*Drug effect*
HR (beats/min)	156 ± 8	156 ± 8 (NS)	136 ± 5	136 ± 5 (NS)
LV vol (ml)	15 1 ± 1 5	13 8 ± 1 6 (p < 0 01)	18 5 ± 1 8	17 [illegible] ± 1 7 (p < 0 01)
LVP (mm Hg)	69 ± 5	76 ± 5 (p < 0 01)	75 ± 3	78 ± 3 (p < 0 01)
LV dP/DT (mm H /sec)	9 4 ± 4[illegible]	1[illegible]99 ± 111 (p < 0 0[illegible])	890 ± 36	960 ± 40 (p < 0 05)
P (Gm /cm)	[illegible]7 9 ± 4 0	28 2 ± 4 1 (NS)	36 0 ± 3 8	35 8 ± 3 7 (NS)
MAX V (muscle lengths/sec)	1 48 ± 0 13	1 81 ± 0 1[illegible] (p < 0 01)	1 16 ± 0 09	1 26 ± 0 08 (p < 0 001)
TTP (msec)	139 ± 7	131 ± 7 (p < 0 05)	155 ± 3	151 ± 4 (NS)
Dur (msec)	33[illegible] ± 18	318 ± 19 (p < 0 01)	3[illegible]7 ± 10	3[illegible]4 ± 1[illegible] (NS)
AP (mm Hg)	89 ± 5	97 ± 6 (p < 0 05)	93 ± 6	10[illegible] ± 6 (p < 0 01)
CBF (ml /min)	107 ± 12	122 ± 14 (p < 0 01)	83 ± 10	85 ± 10 (NS)
A VO (ml /100 ml)	8 3 ± 0 7	9 0 ± 0 7 (NS)	9 6 ± 1 0	10 2 ± 1 0 (p < 0 0[illegible])
MVO (µl/beat/100 Gm)	43 8 ± 3 7	54 5 ± 4 2 (p < 0 01)	45 4 ± 3 4	49 8 ± 3 4 (p < 0 01)

HR = heart rate LV vol = left ventricular volume LVP = peak left ventricular pressure LV dP/dt = maximum rate of rise of left ventricular pressure P = peak left ventricular wall stress MAX V = maximum observed contractile element velocity at lowest common levels of wall stress TTP = time from onset of left ventricular contraction to peak wall stress Dur = duration of contraction AP = mean systemic arterial perfusion pressure CBF = coronary blood flow A VO = coronary arteriovenous oxygen difference MVO = myocardial oxygen consumption numbers in parentheses are p values for statistical comparison of control versus drug effects (NS) = no significant difference between control and drug effect all values are mean ± SEM

Norepinephrine (2×10 µmoles/Kg /minute) was infused intraarterially via a cannula inserted into a carotid artery and advanced so that the tip was in the ascending aorta just above the aortic valve Ouabain (4×10 µmoles/Kg) was injected intravenously over 30 to 60 seconds As the effects of norepinephrine or ouabain were observed the volume of saline in the left ventricular balloon usually had to be reduced in order to maintain peak calculated LVS constant within each experimental animal Oscillographic tracings and blood samples were then obtained during steady state conditions of drug effects (5 to 10 minutes after beginning norepinephrine infusion or 15 to 20 minutes after ouabain administration)

At the end of each experiment the weight of the left ventricle including the septum was obtained after removal of the atria and the free wall of the right ventricle Assuming a specific gravity of 1 this weight was used as the actual muscle volume of the left ventricle Values of LVP and LV dP/dt were determined at 10 msec intervals from two successive beats during each control and drug induced period and were utilized for digital calculation of left ventricular wall stress and contractile element velocity (V_{CE}) In an isovolumic contraction V_{CE} is equal to the rate of lengthening of the series elastic component (V_{SE}) and V_{SE} is directly proportional to the rate of stress development (dS/dt) and inversely related to the stiffness of the series elastic component (dS/dl) Thus V_{CE} in muscle lengths (or circumferences) per second was calculated as $V_{CE} = V_{SE} = (dS/dt)/(dS/dl)$ where $dS/dl = 28S$[27] Calculated values of simultaneous left ventricular wall stress and V_{CE} were plotted to obtain stress-velocity curves and the maximum observed V_{CE} at the lowest common level of left ventricular wall stress in each animal (MAX V)

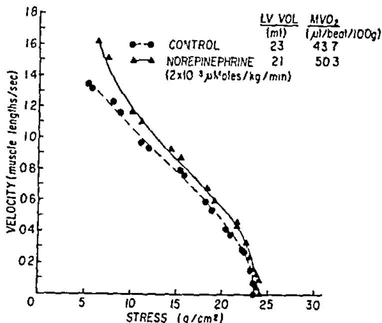


Fig 1 Representative stress-velocity relations in a dog before and after norepinephrine VELOCITY = contractile element velocity STRESS = left ventricular wall stress LV VOL = left ventricular volume MVO = myocardial oxygen consumption values of MAXV (1 32 and 1 62 muscle lengths/sec control and norepinephrine respectively) were obtained at common left ventricular wall stress of 6 2 g/cm

Methods

Fourteen mongrel dogs of either sex weighing from 16 3 to 32 2 kilograms were anesthetized with intravenous pentobarbital sodium (30 mg / Kg) Respiration was maintained with a positive pressure respirator and the heart and great vessels were exposed through a midline sternotomy The experimental preparation has been described previously [11] Following the administration of heparin sodium (750 U /Kg) the experimental animal was placed on total cardiopulmonary bypass Venous blood from the superior and inferior venae cavae and from the right ventricle was drained to a reservoir oxygenated passed through a heat exchanger and pumped retrogradely into a femoral artery The hilum of each lung was securely ligated and the lungs were removed distal to the ligatures A thin latex balloon attached to a wide bore metal cannula was placed in the left ventricle through the left atrium, the metal cannula emerged from the left ventricle through a small stab wound in the left ventricular apex A plastic disc was wedged in the left ventricular outflow tract and a second plastic disc was sutured into the mitral annulus to keep the balloon within the left ventricular cavity Left ventricular isovolumic contractions were produced by placing known amounts of saline into the balloon through one arm of a three-way stopcock connected to the metal cannula Left ventricular pressure (LVP) was measured through the metal cannula by a Statham P23Db pressure transducer attached to the other arm of the three way stopcock Systemic arterial pressure was measured from the left subclavian artery The sinoatrial node was crushed and heart rate was maintained constant in each experimental animal by electrical pacing of the right atrium To eliminate reflex autonomic effects on the heart both vagus nerves were sectioned in the neck and the stellate ganglia were removed bilaterally

The first derivative of left ventricular pressure with respect to time (LV dP/dt) was determined using an active differentiator (Electronic Gea Inc , Model UD 20B) Left ventricular wall stress (LVS) expressed as the tangential tension per unit cross sectional area of the left ventricular wall, was continuously calculated by an analog computer (Electronic Associates Inc , Model TP 20) Assuming a thick walled spherical model LVS in Gm /cm was calculated as $Pr_i/(r_o^2-r_i^2)$ where P = left ventricular pressure in Gm /cm r_i = internal radius of the left ventricular cavity in cm and r_o = internal radius of the left ventricular cavity plus left ventricular wall thickness in cm [5, 25] Systemic arterial pressure LVP, LV dP/dt LVS and the electrocardiogram were recorded on a direct writing oscillograph at a paper speed of 100 mm /sec

Coronary blood flow was determined by timed collection of the venous effluence from the drainage tube in the right ventricle Coronary venous blood samples were also obtained from this drainage tube Duplicate determinations of oxygen content of each arterial and coronary venous blood sample were obtained manometrically by the method of Van Slyke and Neill [6] MVO (expressed as µl/beat/100 Gm left ventricular weight) was calculated as the product of coronary blood flow times the coronary arteriovenous oxygen content difference divided by heart rate

In each experimental animal control oscillographic tracings and control arterial and coronary venous blood samples were obtained simultaneously during steady state conditions Following the control period norepinephrine or ouabain was administered Six dogs received only ouabain six dogs received only norepinephrine and two animals received ouabain after norepinephrine

Table II Slopes of linear regression of myocardial oxygen consumption (MVO) versus maximum observed contractile element velocity at lowest common wall stress (MAX V)

Intervention	Slope
Ouabain (8)	45 4 ± 12 5
Norepinephrine (8)	34 5 ± 5 6
Increasing heart rate† (8)	10 0 ± 1 5‡

Numbers in parentheses indicate number of dogs
U ts f slopes are (µl/beat/100 Gm)/(muscle le gths/se) values g re mean ± SEM
†Values for increasing h art rate we obtained f om a previous tudy The slope was calc lated after subtracting basal O cons mption from total O consumpt on sin e basal O consumpti per beat decre ses w th in reasing heart t (see Boerth t al) Basal O consumpt on was t subtra ted from total O con umpti f ouaba n or norep nephrine since h art r te d d not ch ng and thus subtracti n of basal O₂ c nsumpti would not change th l pes of th egression f r those interv nt ons
‡S gnifi ntly different from slope f uabain at p < 0 0? a d gnifi c ntly d ff re t from slope for nor pin phrine at p < 0 001

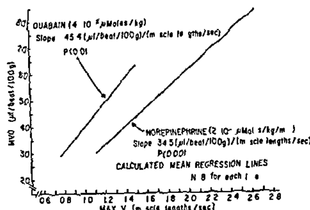


Fig 3 Calculated mean regression lines of myocardial oxygen consumption versus inotropic state for ouabain and norepinephrine See text for derivation of mean regression lines *MVO* = myocardial oxygen consumption *MAX V* = maximum observed contractile element velocity at lowest common level of left ventricular wall stress *N* = number of dogs *p value* indicates significance level for a positive slope greater than zero

MAX V for ouabain and norepinephrine were each statistically compared by t test to that slope obtained by altering heart rate The results in Table II show that the mean slope produced by increasing heart rate was significantly less than the slope for either norepinephrine or ouabain

Discussion

Whereas it is well known that catecholamines increase myocardial oxygen consumption confusion has existed in the past as to the oxygen cost of cardiac glycosides and aglycones In 1912 Rohde and Ogawa[9] reported that in isovolumically contracting cat hearts strophanthidin produced an increase in MVO which was closely proportional to the increase in cardiac work produced by that drug Other early workers using dog heart-lung preparations reported either a decrease[2] no change or an increase in MVO after administration of cardiac glycosides More recent studies have shown that these agents either increase or produce no change in MVO

The results of the current study certainly agree with previous investigations showing increased MVO associated with the positive inotropic effect of norepinephrine In addition our results indicate that the positive inotropic effect of cardiac glycosides is also accompanied by increased myocardial oxygen demands (Table I Figs 2 and 3) These latter results might seem to be at variance with other reports which showed cardiac glycosides or aglycones to either decrease or not change MVO₂ However in most of the previous studies involving whole heart preparations there was no control over the amount of stress or tension generated within the left ventricle and it has been shown that cardiac glycosides and aglycones decrease left ventricular end diastolic volume in the intact heart under conditions of constant aortic pressure and heart rate[15] [21] thus decreasing peak left ventricular stress Since stress development is a major determinant of MVO a fall of peak left ventricular stress in the previous studies would have tended to decrease MVO, and this could easily have obscured a change in MVO₂ associated with increased velocity of contraction Coleman has shown that when developed stress is maintained constant in cat papillary muscle preparations (either by changing initial length in isometrically contracting muscles or at constant afterload in isotonically contracting muscles) acetylstrophanthidin increases both MVO and velocity of contraction Thus if one considers the important influence of stress development upon MVO there is good correlation between the present results and the findings of previous investigations and all this information together strongly indicates that the cardiac glycosides and aglycones increase MVO in association with increased velocity of myocardial contraction

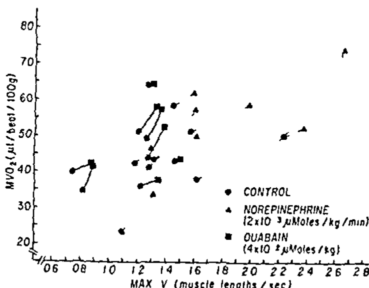


Fig 2 Effects of norepinephrine and ouabain on myocardial oxygen consumption and inotropic state in individual dogs MVO_2 = myocardial oxygen consumption MAX V = maximum observed contractile element velocity at lowest common level of left ventricular wall stress

was used to characterize the inotropic state of the heart

For each animal the slope and Y intercept of the linear regression of MVO (in µl/beat/100 Gm left ventricular weight) versus MAX V were calculated using the method of least squares The slopes and Y intercepts of individual experiments were averaged for each drug to obtain a mean regression of MVO versus MAX V for norepinephrine and a separate mean regression for ouabain All statistical comparisons were made using t tests with a criterion of significance of $P < 0.05$

Results

The effects of norepinephrine and of ouabain on the dynamics of left ventricular isovolumic contraction are shown in Table I Each of these drugs produced an increase in peak LVP so that to maintain peak calculated wall stress constant in each animal, left ventricular volume usually had to be reduced Despite the reduction of left ventricular volume maximum LV dP/dt was increased by both norepinephrine and ouabain, but norepinephrine had the greater effect upon this parameter

The increased LV dP/dt indicated that each of these drugs augmented the velocity of myocardial contraction Fig 1 shows representative stress-velocity curves obtained from a dog before and after norepinephrine administration and similar curves were seen in the dogs receiving ouabain Each of these agents produced an increase in MAX V together with a simultaneous increase in MVO and these increases occurred at a time when peak left ventricular wall stress (P X intercept) was not significantly different than during the control period (Table I)

Fig 2 shows the simultaneous changes in MVO and MAX V for all the dogs receiving either norepinephrine or ouabain In every case MVO and MAX V were increased by norepinephrine or ouabain but in two of the dogs receiving ouabain the changes were very small Although the enhanced MVO was greater with norepinephrine than it was with ouabain norepinephrine also produced a larger augmentation of inotropic state as characterized by increased values of MAX V (Table I, Fig 2) Therefore, it was necessary to determine whether there was a difference between norepinephrine and ouabain in the increase in MVO for an equal increase in inotropic state

Linear regression of MVO on MAX V was calculated for each of the 16 individual observations using steady state values during the control and drug induced periods as the experimental points The values of the slopes and Y intercepts for these regressions were then averaged to obtain separate calculated mean regression lines for norepinephrine and for ouabain as shown in Fig 3 The positive slope of this relationship for norepinephrine was 34.5 ± 5.6 µl beat⁻¹ 100 Gm⁻¹/muscle lengths sec⁻¹ (mean ± SEM) and that for ouabain was 45.4 ± 12.5 µl beat⁻¹ 100 Gm⁻¹/muscle lengths sec⁻¹ (mean ± SEM) Each of these slopes was highly significant ($p < 0.001$ for norepinephrine and $p < 0.01$ for ouabain) indicating that the augmented inotropic state (i e increased MAX V) produced by each of these agents was associated with a significant increase in MVO_2 However there was no significant difference between the slopes of these mean regressions for ouabain and norepinephrine Thus, for an equal increase in inotropic state at constant peak wall stress ouabain increased MVO_2 to the same extent as did norepinephrine

The second purpose of this investigation was to determine whether there is a difference in the myocardial oxygen cost of increased inotropic state produced by pharmacologic agents (ouabain and norepinephrine) as compared to that produced by increasing heart rate In order to make this comparison the slopes of MVO versus

pport to the concept that inotropic state is an important determinant of myocardial oxygen consumption

It has become apparent that in heart muscle neither Vmax (extrapolated velocity of contraction at zero stress) nor the maximum observed velocity of contraction is an index of inotropic state entirely independent of initial muscle length or preload However the results of Parmley and co workers show that in the two element or Voigt three element model of isometric contraction in cat papillary muscles changes in initial muscle length (on the ascending limb of the length-stress curve) produce no distinct differences in calculated velocity of contraction at common low levels of stress In the current study contractile element velocity was calculated using total stress rather than developed stress *(see Methods section)* so that our results are indicative of a two-element or Voigt three element model of heart muscle In addition the index of inotropic state was not an extrapolated Vmax but rather it was the contractile element velocity at the lowest common level of wall stress in each animal (MAX V) Furthermore even if the values of MAX V were influenced more by changes in initial muscle length as in the Maxwell three element model of heart muscle this influence would be to decrease MAX V since left ventricular volume was reduced during the drug effects Thus in that case the observed increases in MAX V would actually have underestimated the augmentation of inotropic state by norepinephrine and ouabain but this would not alter the basic conclusions of the study

It is concluded that augmented inotropic state produced by either norepinephrine or ouabain is associated with increased myocardial oxygen consumption Furthermore there is no significant difference between the effects of norepinephrine and ouabain on this relationship so that for an equal increase in inotropic state ouabain increases myocardial oxygen demands to the same extent as does norepinephrine However when the results produced by these pharmacologic agents are compared with results obtained by altering heart rate it appears that the enhanced inotropic state produced by increasing heart rate is associated with a smaller increase in myocardial oxygen consumption than occurs with either norepinephrine or ouabain

Summary

The purpose of this study was to compare the myocardial oxygen cost of augmented inotropic state produced by ouabain norepinephrine or increased heart rate This problem was examined in dogs using an isovolumically contracting left ventricular preparation Inotropic state was measured as the maximum observed contractile element velocity at the lowest common level of wall stress (MAX V) Peak left ventricular wall stress was maintained constant in each dog so that it would not influence changes in myocardial oxygen consumption (MVO_2) Ouabain (4×10^{-2} μmoles/Kg) and norepinephrine (2×10^{-3} μmoles/Kg /minute) always augmented inotropic state (MAX V) and increased MVO_2 The positive slopes of the regression of MVO on MAX V for ouabain (45 4 ± 12 5 μl/beat/100 Gm /muscle length/sec mean ± SEM) and norepinephrine (34 5 ± 5 6 μl/beat/100 Gm /muscle length/sec mean ± SEM) were not significantly different indicating that for an equal augmentation of inotropic state ouabain increases myocardial oxygen demands to the same extent as does norepinephrine When the results with ouabain or norepinephrine were compared to results obtained by altering heart rate it was found that increasing inotropic state by these pharmacologic agents is more costly in terms of myocardial energy demands than when inotropic state is enhanced by increasing heart rate

The authors wish to express their sincere appreciation to Mr Richard Evans Mr Thomas Vondersmith and Mr Robert Hester for their excellent technical assistance and to Mrs. Kathleen Goralski for her typing of the manuscript

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Since the positive inotropic effects (i e increased velocity of contraction) produced by catecholamines and by cardiac glycosides and aglycones are both accompanied by increased MVO it is of basic importance to know whether the increased oxygen demands produced by these two groups of agents are the same or different for an equal increase in inotropic state The current study shows that in the isovolumically contracting canine left ventricle norepinephrine and ouabain each produce a significant positive linear relationship between MVO and inotropic state as defined by MAX V (Fig 3) Furthermore this study shows that there is no significant difference in the slope of this relationship for ouabain compared to that for norepinephrine indicating that ouabain (and presumably other cardiac glycosides and aglycones) increases MVO to the same extent as does norepinephrine for an equal increase in inotropic state

It was suggested in an earlier study [11] using the same experimental preparation, that the increased MVO associated with increased inotropic state might be less when inotropic state is augmented by increasing heart rate as compared to norepinephrine In order to examine this possibility more closely the slopes of the regression of MVO versus MAX V for ouabain and norepinephrine were each statistically compared to that slope obtained previously by increasing heart rate [11] As shown in Table II the slope produced by increasing heart rate was significantly less than the slope for either norepinephrine or ouabain Thus, there appears to be a basic difference between the positive inotropic effect of increasing heart rate and the positive inotropic effect of norepinephrine and ouabain such that the augmented inotropic state produced by increasing heart rate is less costly in terms of myocardial energy demands The reason for such a difference is unknown at present The difference is probably not due to a metabolic effect of the drugs which is independent of contraction such as direct stimulation of intermediary metabolism or uncoupling of oxidative phosphorylation since pharmacologic concentrations of either catecholamines [9,11] or cardiac aglycones [4,21] do not alter resting energy utilization of myocardium It is possible that basal oxygen consumption per unit time might decrease at higher heart rates and this would significantly increase the slope of contraction dependent oxygen consumption versus MAX V for increasing heart rate thus eliminating the differences in the slopes for increasing heart rate and the positive inotropic drugs Although this possibility intuitively seems wrong it can be neither proven nor disproven experimentally However, a more likely explanation is that increasing heart rate and these positive inotropic drugs may have different effects upon mechano-chemical coupling in heart muscle

In order to be sure that the changes in myocardial oxygen consumption observed in the present study were associated only with changes in velocity of contraction it is important to determine whether other factors might have influenced the results The observed increases in MVO were not due to changes in peak left ventricular wall stress because left ventricular volume was reduced in order to maintain peak calculated wall stress constant between the control and drug induced periods in each dog (Table I) Neither can the increased MVO be explained by increased integrated stress since time to peak wall stress and the duration of contraction were not altered by ouabain and were actually decreased slightly by norepinephrine The observed drug effects were not due to changes in heart rate because heart rate was held constant within each animal Myocardial fiber shortening against a load to produce external work has also been shown to influence myocardial energy utilization [1,3] In the isovolumic left ventricular preparation of the present study no external work was produced although there probably was a small amount of fiber shortening associated with a change in shape of the ventricle during contraction [34] However the small amount of fiber shortening would have been similar during the control and drug induced periods in each dog and therefore would not have influenced the results In addition Pool and colleagues[7] have suggested that fiber shortening *per se* is not a determinant of myocardial energy utilization Finally, it is unlikely that the observed increases in MVO were due to changes in basal or resting oxygen consumption since catecholamines [11] and cardiac aglycones [9] have been shown to not alter resting energy utilization in isolated myocardial preparations Thus the positive relationship between MVO and velocity of contraction (inotropic state) in the present study appears to be valid and lends addition

ardiac dose response relationship for ntravenously infused glucagon in normal ntact dogs and men*

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The pancreatic hormone glucagon has been known to have cardiac effects since 1960 when Farah and Tuttle reported that the inotropic and chronotropic effects on the heart that had been attributed to insulin were due to contamination with glucagon Since that finding there have been numerous studies of glucagon s cardiovascular effects in a number of experimental animal models and in men in various states of health and glucagon has been used clinically as a cardio tonic agent with disparate results The mecha nism of its action on the heart remains unclear There is substantial suggestive evidence that its action is mediated by cyclic AMP although recent studies in rabbits guinea pigs and fetal mice have reported an apparent dissociation between the inotropic effects of glucagon and the adenyl cyclase system In some patients with chronic congestive heart failure and cats with chronic right sided failure due to pulmonary artery banding failure of glucagon to exert a cardiac effect has been demonstrated[7] Conse quently a clearer understanding of glucagon s mechanism(s) of action on the heart may prove useful by providing clues to cellular abnormalities important in cardiac decompensation

Fig 1 Mean plasma glucagon levels at varying doses in normal men and dogs

Surprisingly the cardiac dose response to glucagon in normal intact unanesthetized ani mals or men has not been elucidated previously Since this is relevant to both its clinical use and its mechanism of action we have studied this

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This w rk was pported in part by the Med al R sea h Service of the V terans Adm nistrat n and th Am ri n H rt Assoc t Texas Affiliate M Osborn w s pported by the Moss H art F unda tion, Dallas, T as.

Recei ed for p blic t on N 1 19 7

Accepted f publ cat M r h 6 19 8

Reprint requests D Th mas C Smith rm V ter ns Adm nistr tion Hospital (111A6) 4500 South La caster R ad D ll s, T xas 5 16.

Presented in part t th meeting of th Southern Secti n f the Americ Feder t n for Clini l Rese rch, New Orl a L Ja u ary 19"6.

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ystem (Smith Kline Ekoline 20A Electronics for Medicine VR 6 Echocardiographic Processor Electronics for Medicine Simultrace VR 6 record r) Systolic time intervals including LV ejection time index (LVETI) pre ejection period index (PEPI) onset of electrocardiographic Q wave to onset of the second heart sound index (Q S_2I) and PEP/LVET were measured according to the methods of Weissler and associates [6] using external transducers (Electronics for Medicine PS 2) for carotid pulse (1 to 30 Hz) and heart sound (30 to 1000 Hz) analysis Blood pressure was obtained by sphygmomanometry and the pressure-rate (double) product was calculated Basal cardiac indices and plasma glucagon levels (PGL) were obtained after administration of normal saline intravenously for 30 to 45 minutes Three infusions of glucagon at rates of 10^{-10} 10^{-9} and 10^{-8} moles/minute (Glucagon for injection USP/Lilly in normal saline) were delivered continuously by infusion pump (Harvard Apparatus Inc) for thirty minutes each followed by a single glucagon bolus of 0 5 mg (five men) or 1 0 mg (five men) Cardiographic and plasma glucagon determinations were made at the end of each infusion and 2 to 7 minutes following the bolus delivery a time previously shown to be associated with maximal cardiac effect

Experiments with intact unanesthetized dogs In five normal dogs weighing 15 to 38 kilograms an electromagnetic aortic flow probe (Zepeda EDP 2 square wave calibrated as previously described [1]) a solid state left ventricular pressure transducer (Konigsberg P 21) and indwelling left atrial and pulmonary artery catheters were surgically implanted The dogs recuperated a minimum of one month They were studied while fasting after reaching the basal state 0 5 to 1 hr after transfer to the laboratory Glucagon was infused intravenously at a rate of 2 7 × 10 1 35 × 10 2 7 × 10 1 35 × 10 2 7 × 10 and 2 7 × 10 moles/minute for 30 minutes per infusion rate followed by a single 2 mg intravenous bolus Heart rate stroke volume left ventricular pressure and the maximum rate of pressure development (dP/dt) were measured

In two of the dogs the 1 35 × 10 moles/minute infusion rate was maintained for 6 hours in order to ascertain if cardiac effects not present during short periods of exposure to pathophysiologic levels would be demonstrated during a more prolonged exposure Hourly hemodynamic and plasma glucagon measurements were obtained

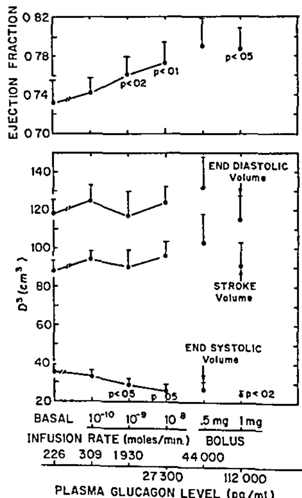


Fig 2 Left ventricular ejection fraction end-diastolic volume end systolic volume and stroke volume at increasing glucagon infusions rates and mean plasma glucagon levels in normal men *Bars* represent one standard error of the mean Values that differ significantly from the values of the basal state *are indicated by the p value*

Since it has been suggested that chronic hyperglucagonemia might occur with chronic congestive heart failure leading to occupation of all available glucagon receptors [3] and hence failure of its cardiac effects one dog received four times daily subcutaneous administration of 1 mg of glucagon for 7 days following the initial glucagon infusion followed by repeat physiologoc evaluation following a 2 mg intravenous injection of glucagon

Plasma glucagon and insulin levels were measured by radioimmunoassay [1, 15] Plasma glucose levels were determined by the glucose oxidase method [6]

Table 1 Hemodynamic indices as a function of glucagon infusion rates in normal men–glucagon infusions rate (moles/minute)

	Basal	*10 ⁹*	*10*	*10 ⁸*	*Bolus .5 mg*	*Bolus 1 mg*
HR	55 9 ± 1 9(10)	56 8 ± 2 2(10)	58 4 ± 3 4(5)	69 9 ± 3 3(5)	67 2 ± 1 7(5)	9,5 ± 6 0(5)
(Min)	–	NS	NS	< 02	< 05	< 01
BP(SYS)	117 ± 3(10)	120 ± 4(10)	112 ± 4(5)	122 ± 5(5)	131 ± 6(5)	128 ± 9(5)
(mm Hg)	–	NS	NS	NS	NS	NS
BP(DIA)	74 ± 3(10)	75 ± 3(10)	72 ± 6(5)	75 ± 7(5)	77 ± 3(5)	70 ± 8(5)
(mm Hg)	–	NS	NS	NS	NS	NS
PRP	65 6 ± 4 0(10)	68 5 ± 4 2(10)	65 6 ± 5 4(5)	93 4 ± 6.9(5)	87 0 ± 4 0(5)	1?3 4 ± 14 8(5)
(Sys BPxHR/100)	–	NS	NS	< 02	< 05	< 01
CO	5 0 ± 0 3(10)	5 2 ± 0 3(10)	5 2 ± 0 3(5)	6 7 ± 0 8(5)	6 4 ± 0 6(5)	8 6 ± 0 (4)
(liters/min)	–	NS	NS	< 10	< 05	< 0?
EDV	118 ± 7(10)	125 ± 8(10)	117 ± 13(5)	124 ± 9(5)	132 ± 16(5)	115 ± 11(4)
(ml)	–	NS	NS	NS	NS	NS
ESV	35 ± 4(10)	33 ± 3(10)	23 ± 4(5)	26 ± 3(5)	27 ± 4(5)	?4 ± ?(4)
(ml)	–	NS	< 05	< 05	NS	< 0?
SV	88 ± 5(10)	92 ± 6(10)	90 ± 9(5)	96 ± 8(5)	103 ± 15(5)	91 ± 1?(4)
(ml)	–	NS	NS	NS	NS	NS
EF	73 ± 2(10)	74 ± 2(10)	77 ± 1(5)	77 ± 2(5)	79 ± 3(5)	79 ± ?(4)
(%)	–	< 10	< 02	< 01	NS	< 05
PWD	10 8 ± 0 4(10)	11 0 ± 0 3(10)	11 5 ± 0 4(5)	13 0 ± 0 6(5)	14 0 ± 0 7(5)	1? 3 ± 1 4( )
(mm)	–	NS	< 05	< 02	< 02	NS
PWV	36 6 ± 1 4(10)	35 5 ± 1 6(10)	38 3 ± 2 4(5)	45 2 ± 2 6(5)	43 1 ± 3 1(5)	41 4 ± 3 1(4)
(mm /sec)	–	NS	NS	< 01	< 02	NS
Q S I	527 ± 3(10)	530 ± 4(10)	522 ± 10(5)	519 ± 3(5)	529 ± 9(5)	531 ± 9(5)
(msec)	–	NS	NS	NS	NS	NS
LVETI	421 ± 3(10)	424 ± 5(10)	423 ± 6(5)	426 ± 4(5)	443 ± 13(5)	436 ± 5(5)
(msec)	–	NS	NS	NS	NS	< 01
PEPI	108 ± 3(10)	104 ± 13(10)	104 ± 13(5)	93 ± 3(5)	86 ± 7(5)	95 ± 6(5)
(msec)	–	NS	NS	< 01	< 01	NS
PEP/LVET	260 ± 009(10)	261 ± 016(10)	248 ± 019(5)	221 ± 012(5)	183 ± 026(5)	204 ± 019(5)
	–	NS	NS	< 02	< 01	< 10
$\bar{V}_{cf}$	1 03 ± 04(9)	1 15 ± 04(8)	1 20 ± 06(5)	1 32 ± 08(4)	1 48 ± 27(5)	1 4? ± 06(4)
(circum ferences/sec)		NS	< 10	< 01	NS	< 01
D to E slope	285 ± 29(10)	290 ± 36(9)	268 ± 45(5)	298 ± 28(5)	308 ± 75(5)	3?9 ± 3?(4)
(mm /sec)	–	NS	NS	NS	NS	NS
Plasma glucagon levels (pg /ml)	226 ± 65(10)	309 ± 109(9)	1930 ± 730(5)	27 300 ± 700(5)	44 000 ± 11 800(5)	11? 000 ± 41 000(5)
	–	<0 1	NS	<0 001	<0 001	<0 001
Plasma insulin levels (U /ml)	9 ± 2(9)	14 ± 4(10)	45 ± 13(4)	76 ± 14(5)	26 ± 8(5)	56 ± 23(5)
	–	NS	NS	<0 02	<0 10	NS
Plasma glucose levels (mg /dl)	65 ± 9(9)	86 ± 2(8)	127 ± 8(5)	98 ± 19(5)	89 ± 10(4)	100 ± 2?(5)
	–	<0 01	<0 001	NS	NS	NS

All values are mean ± S E M
Values in parenthesis are number of subjects

cardiac dose response of glucagon in dogs and men

Materials and methods

Experiments in normal men Ten paid informed volunteers all young men, mean age 22 with normal cardiac history, physical exam and electrocardiogram were studied non invasively in the supine position and the post absorbtive state Measurements of the echocardiographic indices of left ventricular function including end systolic (ESV) end diastolic (EDV) and stroke volumes (SV) ejection fraction (EF) mean posterior wall velocity (PWV) and displacement (PWD) rate of mitral valve opening (D to E slope) were made by the methods of Feigenbaum[8] and mean circumferential fiber shortening rate ($\bar{V}_{cf}$) were made by the methods of Cooper and colleagues[9] using a 2 25 MHz transducer (Smith Kline C 14) and an M mode strip chart echocardiographic

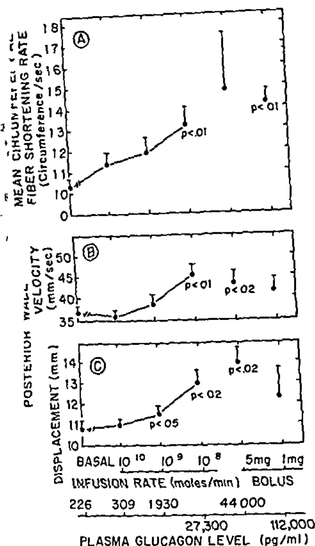


Fig 3 Mean circumferential fiber shortening rate ($\bar{V}_{CF}$) left ventricular posterior wall displacement and mean velocity in normal men at increasing infusion rates and mean plasma glucagon levels in normal men *Bars* represent one standard error of the mean Values that differ significantly from the values of the basal state *are indicated by the p value*

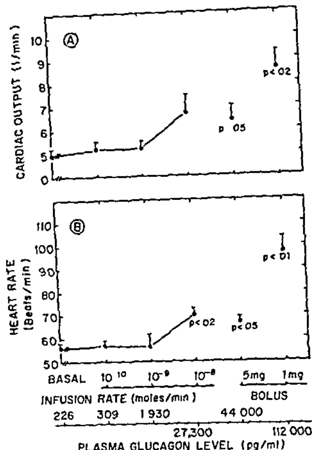


Fig 4 Heart rate and cardiac output in normal men at increasing glucagon infusion rates and mean plasma glucagon levels *Bars* represent one standard error of the mean Values that differ significantly from the values of the basal state *are indicated by the p value*

diographic assessment of left ventricular performance demonstrated small yet significant evidence for an enhanced inotropic state at a mean plasma glucagon level of 2 000 pg/ml a level only slightly higher than those reported in a number of stressful pathologic states such as infections[1] ketoacidosis burns trauma[20] and myocardial infarction [2] The small (5 per cent) but significant increase in ejection fraction was due to a significant decrease in end systolic volume without a statistically significant change -diastolic volume (Fig 2) At this glucagon level there was also a significant increase in posterior wall displacement (Fig 3) The small increases in stroke volume posterior wall velocity and V_{CF} at this infusion level were not significant With the next infusion level associated with a mean plasma glucagon concentration of 27 300 pg/ml the magnitude of the chronotropic and inotropic response were almost as great as those observed following the injection of a bolus of glucagon There were significant changes in ejection fraction and posterior wall displacement and velocity at this level Heart rate and cardiac output were modestly raised at mean glucagon levels of 27 300 pg/ml and above (Fig 4) The increase in cardiac output was almost exclusively secondary to the chronotropic effect since stroke volume was only slightly raised The D to E slope of the anterior leaflet of the mitral valve was not

Table II Hemodynamic measurements in dogs at various glucagon infusion rates (moles/minute)

	Basal	*Infusion rate*						
		2 7 × 10 ¹	*1 4 × 10*	*2 7 × 10 ¹*	*1 4 × 10*	*2 7 × 10*	*2 7 × 10 ⁸*	*2 mg bolus*
HR (min)	92 ± 14 (5) –	99 ± 18 (5) NS	101 ± 19 (4) NS	95 ± 10 (5) NS	104 ± 14 (4) NS	98 ± 11 (5) NS	138 ± 5 (5) < 02	141 ± 16 (5) < 05
SV (ml)	22 5 ± 4 3 (5) –	22 7 ± 4 4 (5) NS	22 3 ± 4 0 (4) NS	22 3 ± 4 4 (5) NS	23 7 ± 5 1 (4) NS	22 3 ± 3 8 (5) NS	21 7 ± 3 0 (5) NS	23 1 ± 3 0 (5) NS
CO (L /min)	2 14 ± 60 (5) –	2 31 ± 62 (5) NS	2 24 ± 89 (4) NS	2 03 ± 75 (5) NS	2 45 ± 1 15 (4) NS	2 12 ± 70 (5) NS	3 01 ± 1 07 (5) < 01	3 42 ± 1 8[illegible] (5) < 01
dP/dt (mm Hg/sec)	2739 ± 135 (5) –	2991 ± 312 (5) NS	2898 ± 70 (4) NS	2672 ± 156 (5) NS	2333 ± 235 (4) NS	2860 ± 156 (5) NS	3710 ± 107 (5) < 01	41[illegible]2 ± 161 (5) < 001
LAP (mm Hg)	6 5 ± 0 6 (5) –	5 3 ± 0 5 (5) NS	6 2 ± 1 0 (4) NS	5 6 ± 1 0 (5) NS	2 9 ± 2 0 (4) NS	2 8 ± 1 0 (5) < 05	1 3 ± 1 6 (5) < 05	1 6 ± 1 1 (5) < 0[illegible]
Plasma glucagon level (pg /ml)	188 ± 40 (5)	201 ± 33 (4)	900 ± 10 (2)	37[illegible]0 ± 1390 (5)	14 580 ± 3870 (4)	31 500 ± 5840 (4)	261 000 ± 61 200 (5)	24 000 ± 80 [illegible]00 (5)
Plasma glucose level (mg /dl)	98 ± 5 (4) –	117 ± 11 (4) NS	100 ± 0 (4) NS	111 ± 12 (4) NS	101 ± 10 (4) NS	99 ± 6 (4) NS	109 ± 4 (4) NS	111 ± [illegible] (4) <0 1
Plasma insulin level (μv/ml)	22 ± 8 (4) –	22 ± 4 (4) NS	34 ± 15 (4) NS	34 ± 19 (4) NS	29 ± 17 (4) NS	39 ± 31 (4) NS	42 ± 30 (4) NS	43 ± 26 (4) NS

All values ± S E M
Value in parenthesis is number of values

Data were analyzed by Student s t test for paired observations

Results

Plasma glucagon levels Plasma glucagon levels increased in a linear fashion (Fig 1) The infusion levels were chosen to deliver approximately equivalent amounts to men and dogs relative to body weight The maximum infusion rate in dogs was 10 times higher than that in man so that the levels achieved after the bolus injection were no greater than with the highest infusion level

In men, somewhat higher plasma glucagon levels were achieved following the bolus than with any infusion level

The infusion levels were chosen to achieve plasma glucagon levels equivalent to those seen physiologically (up to 350 mg /ml) and pathophysiologically (400 to 1 500 pg /ml) as well as those achieved following the intravenous injections (1 to 10 mg) and infusions (1 to 16 mg /hr) that have usually been employed for cardiovascular effects

In men and dogs infusion of approximately 10 ¹² moles/min /Kg (10 ¹⁰ moles/minute for men and 2 7 × 10 ¹¹ moles/minute for dogs) hardly elevated the plasma levels above the basal level A tenfold higher infusion rate led to levels near those seen pathophysiologically At a rate of 10 ⁸ moles/minute for men (2 2 mg /hr) and 2 7 × 10 ⁹ moles/minute for dogs (0 8 mg /hr) the infusion rate was in the range utilized clinically levels approximately 10 times pathophysiologic and 100 times basal were attained At the final infusion rate in dogs, and following the bolus injection in both men and dogs also at doses frequently employed clinically the levels were tenfold higher again

In both men and dogs there were predictable small increases in both plasma glucose and insulin following glucagon infusion (Tables I and II)

Experiments in normal men In men echocar

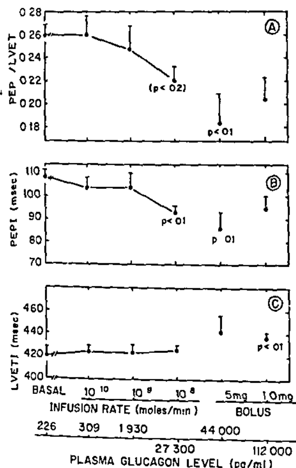


Fig 5 Systolic time intervals in normal men at increasing glucagon infusion rates and mean plasma glucagon levels Left ventricular ejection time index *(LVETI)* Pre ejection period index *(PEPI)* and the *ratio PEP/LVET* are shown *Bars* represent one standard error of the mean Values that differ significantly from the values of the basal state *are indicated by the p value*

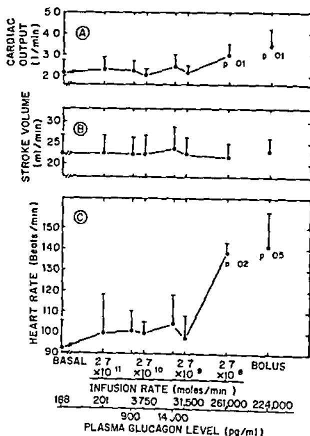


Fig 6 Cardiac output stroke volume and heart rate for intact unanesthetised dogs at increasing glucagon infusion rates and mean plasma glucagon levels *Bars* represent one standard error of the mean Values that differ significantly from the values of the basal state *are indicated by the p value*

cant increase in the inotropic state of the heart Although these disorders are associated with a hyperactive circulatory state it is unlikely that hyperglucagonemia plays a major role in the generation of the hyperkinetic state since the measured changes were so slight at this level and the much more efficacious catecholamines are also present in increased amounts in these states At a mean glucagon level of 27 300 pg /ml which was achieved with 30 minutes of infusion with 10 moles/minute (2 2 mg /hr) the inotropic and chronotropic changes were nearly equal in magnitude to the maximal changes seen in this study following a bolus injection of 0 5 or 1 mg

While gastrointestinal symptoms in man prevent absolute confirmation of the minimal dose necessary to achieve maximal cardiovascular responses the half maximal serum concentration appears to be approximately 10 ^{9} M (35 000 pg / ml)

Nausea and vomiting are the chief problems limiting the use of glucagon as a cardiotonic agent They were rare at an infusion rate of 10 ^{9} moles/minute but common following a 1 mg bolus injection Since it appears possible in normal men to achieve nearly maximal cardiac effects with infusion of 10 ^{8} moles/minute (0 2 mg /minute) of glucagon with virtually no gastrointestinal side effects achieving higher levels may be unnecessary and undesirable However the disparate responses to glucagon in a heterogeneous population makes it necessary to apply this conclusion to patients with cardiac disease with caution

Whether the tenfold lower threshold for cardiac effect in men compared to dogs is a real

Table III

Threshold of cardiac effects of glucagon in normal men			
Infusion level (moles/min)	1 × 10	1 × 10	1 mg bolus
Mean plasma glucagon level (pg /ml)	1 930	27 300	112 000
Index of cardiac performance	ESV	HR	LVETI
	EF	CO	
	PWD	PEPI	
	V_{cf}	PEP/LVET	
		PRP	
Threshold of cardiac effects of glucagon in normal unanesthetized dogs			
Infusion level (moles/min)	2 7 × 10		2 7 × 10
Mean plasma glucagon level (pg /ml)	31,500		261 000
Index of cardiac performance	LVEDP		HR
			CO
			LV dP/dt

changed significantly at any glucagon level, although this measurement has been found to correlate with the cardiac output [3]

Systolic time intervals were less sensitive for detection of the cardiovascular effects of glucagon than the echocardiographic measurement of ejection fraction and posterior wall displacement At a mean plasma glucagon level of 27,300, PEPI and PEP/LVET were significantly shortened (Fig 5) LVETI was not significantly increased until a mean plasma glucagon level of 112,000 pg /ml was reached following the bolus injection Q S$_2$I was not significantly changed at any level of hyperglucagonemia

Neither the systolic nor the diastolic blood pressure was significantly changed at any level (Table I) Due to the chrontropic effect the pressure-rate product was significantly raised at plasma glucagon levels of 27 300 pg /ml and above

Experiments in intact unanesthetized dogs In dogs the threshold for cardiac stimulation was higher than in man The earliest detectable significant change was a drop in left atrial mean pressure, which occurred at the 2 7 × 10 $^{-9}$ moles/minute infusion rate, corresponding to a glucagon level of 31,500 pg /ml (Table II) As in man there was no significant change in the stroke volume at any level Heart rate and consequently cardiac output were significantly elevated at glucagon levels of 224,000 and 261 000 pg /ml (Fig 6) The rate of rise of left ventricular pressure also showed no change until a mean glucagon level of 224,000 pg /ml was reached (Fig 7)

Both dogs that received a 6 hour constant infusion of glucagon maintained a hyperglucagonemic state, one from 500 to 3 300 pg /ml and the other from 3 200 to 4,100 pg /ml Neither demonstrated detectable inotropic or chronotropic effects

The dog that was subjected to a chronic hyperglucagonemic state for one week had a cardiac response to a repeat injection of 2 mg of glucagon that was similar in magnitude to that of the earlier response (heart rate increased 11 per cent after one week compared to 18 per cent before and a 53 per cent increase in LV dP/dt after one week compared to 35 per cent before)

Discussion

This study defines for the first time the cardiac dose response to glucagon in normal unanesthetized men and dogs The cardiovascular effects of glucagon reported here are generally in agreement with the results of previous studies with a modest but significant chronotropic and inotropic response While there was a modest rise in blood pressure, it did not reach statistical significance whereas others using only higher doses of glucagon have found significant increases in systolic and diastolic pressure levels The failure of the small increase in stroke volume to reach a statistically significant level is in agreement with some studies and in disagreement with others As might be anticipated from the common clinical practice of administering very large doses of glucagon the threshold for any cardiac effect is high in both men and dogs (Table III) However in men at a plasma glucagon level of about 2 000 pg /ml which is only slightly greater than that reported in a number of stressful pathologic states there was evidence of a small but signifi

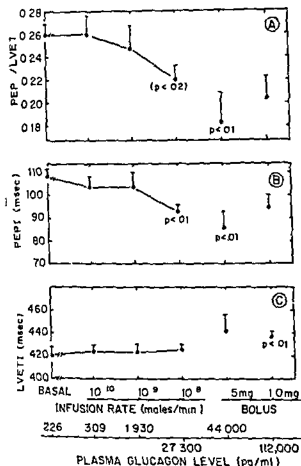


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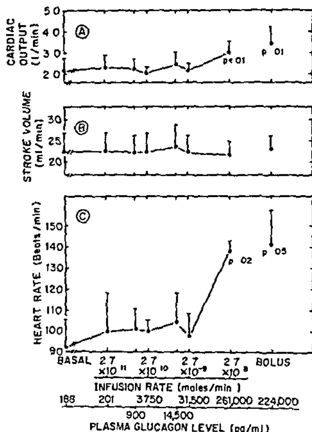


Fig 6 Cardiac output stroke volume and heart rate for intact, unanesthetised dogs at increasing glucagon infusion rates and mean plasma glucagon levels *Bars* represent one standard error of the mean Values that differ significantly from the values of the basal state *are indicated by the p value*

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Whether the tenfold lower threshold for cardiac effect in men compared to dogs is a real

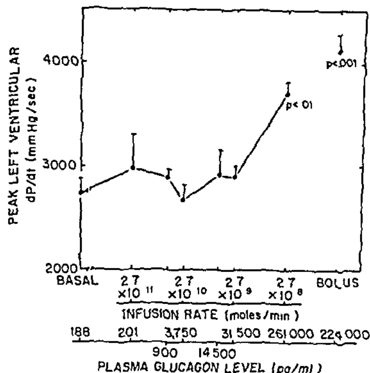


Fig 7 Peak rate of left ventricular pressure rise in intact unanesthetised dogs at increasing glucagon infusion rates and mean plasma glucagon levels *Bars represent one standard* error of the mean Values that differ significantly from the values of the basal state *are indicated by the p value*

difference or an apparent one due to the different techniques that were employed to assess the response cannot be stated with certainty The magnitude of the difference favors a true difference

Since normal men rarely come to diagnostic cardiac catheterization the dose response relation was determined non invasively by means of systolic time intervals and echocardiography This study provides evidence that non invasive assessment of cardiac performance is satisfactory for the determination of the effect of pharmacological interventions in normal subjects Echocardiographic evaluation especially of wall motion and ejection fraction, appears to be more sensitive than determination of systolic time intervals

Summary

The mechanism of glucagon s cardiac effects is not well understood As the cardiac dose response to glucagon in intact animals has not been elucidated, this was determined in normal men and dogs In man heart rate blood pressure systolic time intervals and echocardiographic indices of ventricular wall motion were determined Plasma glucagon levels (PGL) were measured by radioimmunoassay Men received 3 glucagon infusions of 10^{-10} to 10^{-8} moles/minute followed by a bolus of 0 5 mg or 1 0 mg Small but significant changes were observed in ejection fraction and left ventricular posterior wall displacement at the 10^{-9} moles/minute infusion rate (mean PGL 1.9 ng/ml), a PGL close to that of some pathophysiologic states such as burns, ketoacidosis and acute myocardial infarction, while cardiac output, heart rate and other indices of cardiac performance were significantly changed only at the 10^{-8} moles/minute and bolus injections Some indices notably stroke volume were unchanged.

In dogs left ventricular (LV) pressure LV pressure derivative (LV dP/dt) and aortic flow were measured with implanted LV solid state pressure transducers and electromagnetic flow probes Dogs received six infusions from 2.7×10^{-11} to 2.7×10^{-8} moles/minute followed by a bolus of 2 mg In dogs significant changes occurred in LV dP/dt at 2.7×10^{-9} moles/minute (mean PGL 31 5 ng/ml) and in heart rate at 2.7×10^{-8} moles/minute only It appears that substantial hemodynamic effects do not appear in man or dogs until PGL 10 to 100 times those seen in pathophysiologic states are achieved Thus it seems unlikely that glucagon contributes substantially to the hyperdynamic circulatory conditions observed in these states Significant hemodynamic response to glucagon was noted in normal men, however, at a PGL less than that achieved by usual pharmacologic doses of glucagon and this lower PGL was not associated with the gastrointestinal symptoms commonly observed clinically

We acknowledge with gratitude the technical assistance of Mrs Arvella Peters and Mr Paul Jordan and the secretarial assistance of Mrs Betty Bibus We are indebted to Dr Roger Unger for the performance of glucagon glucose and insulin assays

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Table I Comparison of paired myocardial O_2 consumption index values* obtained in five preparations with constant heart rate of 120/minute at regular and bigeminal rhythm before and after coronary artery occlusion (CAO)

	Regular rhythm	*Bigeminy R R 300 msec*	*Mean difference*	*p*
Control	8.81 ± 0.54	10.89 ± 0.95	2.07 ± 0.[illegible]	NS
CAO	9.70 ± 0.75	10.38 ± 0.70	0.68 ± 0.44	NS
Mean difference	0.89 ± 0.60	−0.50 ± 0.70		
p	NS	NS		

*MVO_2I in ml/minute 100 Gm LV
†Abbreviations NS = non significant R R = coupling interval

Table II Comparison of paired myocardial O_2 consumption index values* obtained in six preparations at constant heart rate of 120/minute and bigeminal rhythm with coupling intervals of 300, 400 and 500 msec (regular rhythm) before and after coronary artery occlusion (CAO)

Coupling interval (msec)	*300*	*400*	*500*	*p‡*
Control	10.67 ± 0.80	10.00 ± 0.57	8.69 ± 0.44	NS§
CAO	10.49 ± 0.51	9.54 ± 0.50	9.44 ± 0.67	NS
Mean difference	−0.18 ± 0.56	−0.47 ± 0.42	0.75 ± 0.17	
p†	NS	NS	NS	

*MVO_2I in ml/minute 100 Gm LV
†p obtained by t test for paired observations
‡p obtained by analysis of variance
§Abbreviations NS = non significant

pCO_2 of blood samples were determined using the Astrup apparatus The hematocrit (HCT) of the arterial samples was also determined Myocardial oxygen consumption (MVO_2) was derived as the product of the CBF and the corresponding arteriovenous oxygen difference (Ca c$\bar{v}O_2$) and was then indexed to 100 Gm of wet left ventricular myocardium (MVO_2I) (vide infra)

Mean pressure ($\overline{AP}$) at the aortic root was set and maintained throughout the experiment at 70 mm Hg by adjusting the resistance of the extracorporeal arterial circuit while adjustment of the capacitance was used to maintain an appropriate wave form Cardiac output (i e venous return pump rate) was set and kept at 120 ml/minute per kilogram of body weight (Kg BW) in all instances except during the studies of the HR effect at constant stroke volume, where the cardiac output was set as the product of stroke volume equal to 1 ml Kg^{-1} BW and the HR Data were recorded on an oscillographic recorder (Honeywell 1612 Denver, Colo)

Twenty seven mongrel dogs were studied In seven of these animals the previously prepared anterior interventricular branch of the left coronary artery was ligated and additional data were obtained after coronary artery occlusion (CAO) The experimental protocols followed were

A Effect of the number of PVDs on MVO_2I In seven preparations with heart rate fixed at 120/minute data were obtained in random order of sequence at regular rhythm and while PVDs with fixed coupling (R R) interval of 300 msec and compensatory pause of 700 msec were introduced at regular penta tetra, tri and bigeminal patterns Thus five data points were obtained in each preparation for constant heart rate of 120/minute and 0 (regular rhythm) 24, 30, 40 and 60 PVDs per minute Individual regression lines of MVO_2I versus number of PVDs per minute were derived and the mean weighted slope for the group was then calculated by multiplying the slope of each line (b_i) by the reciprocal square of its standard error ($w = 1/sb_i^2$) and dividing the sum of products ($\Sigma w b_i$) by the sum of the weights (Σw)

In five of the seven preparations with CAO data were obtained before and after CAO at a rate

of 120/minute with both regular and bigeminal rhythm (60 PVDs/minute with 300 msec R R interval) Statistical evaluation of these data was performed by the t test for paired observations

B Effect of coupling interval of PVDs on MVO I In nine preparations with heart rate of 120/minute half of the depolarizations were induced prematurely in bigeminal pattern Then the coupling interval (R R) of these PVDs was changed in steps multiple of 50 msec at random order from 500 msec (regular rate of 120/minute) to 190 to 230 msec (paired pulse stimulation) while adjustments for proper full compensatory pause were made Four to eight data points were obtained within this range of R R intervals from each preparation and individual regression lines of MVO I versus R R were computed by regression analysis Then the mean weighted slope for the group was calculated as described

In six of the seven preparations with CAO data were obtained before and after CAO at heart rate of 120/minute and bigeminal rhythm at R R intervals of 300 400 and 500 msec These data were evaluated by analysis of variance for the coupling interval effect and by the t test for paired observations for the CAO effect

C Effect of heart rate The effect of heart rate on MVO I was first studied in a control group of three preparations by changing HR in random sequence among the rates of 90 120 150 and 180/minute Initially CO was kept constant at 120 ml /minute Kg BW Then at each HR the CO was adjusted in order to maintain a constant SV of 1 ml Kg BW During the constant SV runs the resistance of the systemic circuit was adjusted to maintain a constant mean aortic root pressure of 70 mm Hg Regression lines of MVO_2I versus HR were obtained at constant SV as well as constant CO The lower magnitude of HR effect on MVO obtained during the constant CO runs could be attributed to the reciprocal decrease of SV with increase in HR but other factors could not be excluded It was therefore hypothesized that if the HR to SV relationship were the sole factor responsible then data obtained at constant SV could be derived from data obtained at constant CO and vice versa through correction for this factor In order to test this hypothesis MVO data obtained at each HR step for constant CO of 120 ml /minute Kg ¹ BW were normalized for constant SV of 1 ml Kg BW

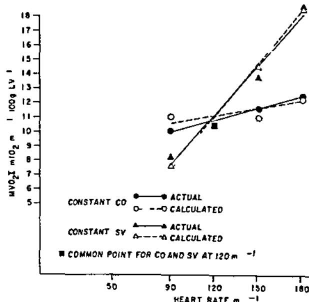


Fig 3 Effect of heart rate on MVO I in three preparations studied both at constant cardiac output (CO) *(dots)* and constant stroke volume (SV) *(solid triangles)* *Solid lines* are regression slopes of the mean values Corresponding regression slopes of calculated values *are indicated with broken lines* Values calculated from actual constant SV data normalized for constant CO *(open circles)* and vice versa *(open triangles)* are shown Actual and calculated data did not differ significantly Error terms have been omitted *(see Table III)* MVO I = myocardial O consumption index

and vice versa The normalization was done as follows Because CO per minute was fixed at 120 ml /minute Kg ¹ BW SV at HR of 120 minute was 1 ml Kg ¹ BW At different HR SV changed with the reciprocal 120/HR Therefore MVO_2 data obtained at constant CO were *divided* by this reciprocal For the opposite correction i e of data obtained at constant SV for constant CO the data were *multiplied* by the same reciprocal The derived data and their regression slopes were then compared with those of actual data

The HR effect was further studied in 14 animals at constant CO by changing HR at two to four of the above heart rates and/or 200/minute In a subgroup of six of these animals MVO I was also determined after CAO at the same heart rates except 180/minute The mean MVO I values were calculated for the available control and post CAO data at each HR step and the regression lines of mean MVO I values versus HR were obtained Post CAO data at each HR step were also compared with their corresponding control data using the *t* test for paired observa

Table III Comparison of effect of heart rate (HR) on myocardial O consumption and left vertncular dynamics at constant cardiac output (CO) and constant stroke volume (SV)

	HR	90	120	150	180			
	no	3	3	3	3	Y = b HR ± b	r	p
	Constant CO	10 09 ± 0 90		11 51 ± 1 06	12 43 ± 1 61	0 027 HR + 1 48	0 98	< 0
MVO I			10 45 ± 1 09					
	Constant SV	8 27 ± 0 98		13 63 ± 1 31	18 57 ± 2 83	0 114 HR − 2 60	0 99	< 0
	Constant CO	8 2 ± 0 04		6 4 ± 0 50	6 1 ± 0 50	−0 023 HR + 10 68	0 94	< 0
LVedp			8 0 ± 0 50					
	Constant SV	6 4 ± 0 60		8 0 ± 0 50	9 5 ± 0 70	0 030 HR + 3 83	0 95	< 0
	Constant CO	1470 ± 88		1260 ± 70	1420 ± 76	−0 90 HR + 1504		NS
LVdp/dt			1380 ± 88					
	Constant SV	1150 ± 72		1630 ± 60	2150 ± 96	10 83 HR + 115	0 99	< 0

Values were obtained at constant CO of 120 ml /minute Kg BW and at constant SV of 1 ml Kg BW At HR of 120/minute all values are identical Abbreviations bo = intercept b = slope LV dp/dt = first derivative of LV pressure (mm Hg/sec) LVedp = LV end-diastolic pressure mm Hg MVO I = myocardial O consumption index (ml O /minute 100 Gm LV) r = correlation coefficient

tions Subsequently, MVO_2I per beat was calculated for each heart rate for both control and post CAO periods and regression lines of mean values were derived Then because CO per minute was fixed at 120 ml /minute Kg ' BW MVO I values per beat were normalized as described to a SV of 1 ml Kg ' BW per beat for all heart rates by multiplying each value by the 120/HR factor Regression lines were then obtained on these normalized data

At the end of the experiment the heart was excised and the left ventricle was weighed in order to index CBF and MVO to 100 Gm to LV myocardium In the animals with ligated coronary artery Evans blue dye was injected distal to the ligature and the stained myocardium was excised and weighed for gross estimation of the ischemic area

Error terms in the data reported are standard error of mean (± SE)

Results

1 MVO effect

A Number of PVDs The effect of number of PVDs with fixed coupling interval on MVO_2I is shown in Fig 1 Individual regression lines obtained from seven preparations had SE less than 0 024 and did not show significant correlation of MVO I with the number of PVDs The weighted mean slope at 95 per cent confidence limits (CL) was 0 003 ± 0 002 ml O /minute 100 Gm ' LV per PVD, and not significantly different from zero

In the group of five preparations where MVO I was measured at regular and bigeminal rhythm before and after CAO no significant difference was found by t test comparison of data paired either for rhythm or for control versus post CAO conditions (Table I) However the difference between regular and bigeminal rhythm at control approached statistical significance ($p < 0 05$?)

B Coupling interval The effect of varying coupling interval of a fixed number of PVDs on MVO I is shown in Fig 2 In the nine preparations with heart rate of 120/minute in bigeminal pattern and varying coupling (R R) interval linear regression analysis of MVO I data versus R R′ showed significant correlation of these variables in only two out of nine preparations ($r = 0 92$ and $0 97$ $p < 0 05$) with only one of the two slopes being significantly different from horizontal (−0 013 ± 0 003) The SE of the regression lines was less than 0 008 and the mean weighted slope was −0 001 ± 0 005 ml O /minute 100 Gm ' LV per ms of R R interval *lengthening* at 95 per cent confidence limits

In the group of six preparations with constant heart rate of 120/minute and bigeminal rhythm MVO I at R R intervals of 300, 400 and 500 msec (regular rhythm) was not found to differ significantly by analysis of variance either before or after CAO Also no statistically significant difference was found between paired pre and post CAO data at any coupling interval (Table II)

C Heart rate effect The effect of HR changes

Table IV Effect of heart rate on coronary and left ventricular dynamics before (C) and after coronary artery occlusion (CAO)

HR	90	120	150	180	200			
no	8	14	12	6	3	Y = b HR ± b	r	p
Control								
MVO I	8 ı5 ± 0 41	8 99 ± 0 24	10 22 ± 0 37	11 01 ± 0 62	11 27 ± 0 25	0?5 HR + 6 30	.98	< 005
LVedp	8 1 ± 0 9	7 9 ± 0 7	6 5 ± 0 6	6.3 ± 0 6	6 0 ± 1 0	– 021 HR + 10 05	96	< 05
LV dp/dt	1415 ± 98	1303 ± 64	1277 ± 68	1336 ± 94	1435 ± 73	17 HR + 1327	–	NS
no	3	6	4	–	3	Y = b HR ± b	r	p
CAO								
MVO I	9 5? ± 1 10	9 58 ± 0 64	10 47 ± 0 80		11 20 ± 0 53	017 HR + 7 88	97	< 05
LVedp	9 7 ± 1 9	7 3 ± 1 3	6 8 ± 1 4		5 7 ± 1 ?	–0 33 + 12 0?	93	NS
LV dp/dt	1500 ± 161	1330 ± 99	1?37 ± 44		1435 ± 73	– 4ı + 1441	–	NS

Abbreviations MVO I = myocardial O sumpt n inde (ml O /minut 100 Gm LV) LVedp = LV end diastolic pressure (mm Hg) LV dp/dt first deri t e of LV pressur (mm Hg/sec)

(90 to 180/minute) on MVO I in the three preparations studied both at constant CO and constant SV conditions is shown in Table III At all HR steps values obtained at constant CO of 120 ml / minute Kg BW and normalized for constant SV of 1 ml Kg BW did not differ significantly by paired t test from values actually obtained at this constant SV (Fig 3) Also values obtained at constant SV of 1 ml Kg BW and normalized for constant CO of 120 ml /minute Kg BW did not differ from actual values obtained at this constant CO The slopes of regression lines obtained from these actual and calculated data did not differ significantly in the individual preparations and for the group however slopes obtained at constant SV were significantly steeper (Fig 3)

The effect of HR changes at constant CO on MVO I and left ventricular dynamics before and after CAO is shown in Table IV Regression lines of the mean MVO I values obtained at each HR were 0 025 ± 0 003 ml O /minute 100 Gm LV per beat of HR increase (r = 0 98 p < 0 005) for the pre CAO data and 0 017 ± 0 003 (r = 0 97 p < 0 05) for the post CAO data (Fig 4) Slopes of these lines were not found to differ significantly T test comparison of paired MVO I data obtained before and after CAO showed no significant difference at any HR

The relationship between these MVO I data expressed per beat and the heart rate is shown in Fig 5a Parallel regression lines with negative slopes –0.35 ± 0 06 and –0 38 ± 0 09 μl O 100 Gm LV per beat of HR increase (r = 0 96 and 0 92 p < 0 001) were derived for the control and post CAO data respectively The apparent curvature was not found statistically significant Lines of same per beat data normalized for constant SV of 1 ml Kg BW as described (Fig 5b) were also parallel but slopes were positive (0 20 ± 0 02 and 0 17 ± 0 05 r = 0 98 and 0 90 p < 0 001 respectively)

2 LVed pressure effect LVed pressure remained below 12 mm Hg in all experiments During PVD introduction variation of LVed pressure on a beat to beat basis resulted from changing duration of the filling period according to the R R interval and the compensatory period but the average values did not change

The small LVed pressure decrease associated with increasing HR at constant CO (Table III) was significant (r = 0 94 p < 0 05) Regression lines with similar slopes (r = 0 96 and r = 0 93) were also derived from the control and post CAO mean data of Table IV In contrast at constant SV the LVed pressure increased with increasing HR (r = 0 95 p < 0 05) (Table III)

3 LV dp/dt effect During PVD introduction LV dp/dt varied on a beat to beat basis as result of R R interval and SV variations associated with the duration of filling period However LV dp/dt values obtained with regular rate immediately after discontinuation of PVDs did not differ significantly from control

Heart rate changes at constant CO resulted in highest LV dp/dt values at HR of 90 and 180/

Table III Comparison of effect of heart rate (HR) on myocardial O consumption and left ventricular dynamics at constant cardiac output (CO) and constant stroke volume (SV)

		HR	90	120	150	180			
		no	3	3	3	3	Y = b HR ± b	r	p
MVO I	Constant CO		10 09 ± 0 90*		11 51 ± 1 06	12 43 ± 1 61	0 027 HR + 7 48	0 93	< .05
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C Heart rate effect The effect of HR changes

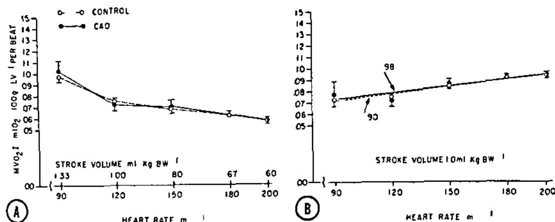


Fig 5 Effect of heart rate on MVO I per beat during control *(circles and broken lines)* and after coronary artery occlusion *(dots and solid lines)* *a* Actual data obtained at constant CO of 120 ml /minute Kg BW *b* Same data normalized for constant SV of 1 ml Kg BW Data did not differ significantly *CAO* = coronary artery occlu ion *MVO I* = myocardial O consumption index

appeared as result of the force–frequency relationship for heart rates above 150 minute while at lower heart rates associated with larger stroke volumes appeared as result of the force–length relationship Since LV dp/dt is affected by pre load changes the contractility effect may have been underestimated at higher heart rates where preload is decreasing On the contrary at lower heart rates where preload is higher contractility was probably overestimated by LV dp/dt

According to these data no significant MVO I effect is expected as result of PVDs with full compensatory pause However increase of HR by 1 beat per minute when minute work is constant is expected to increase MVO by a statistically significant 0 025 ml O /minute 100 Gm LV and up to 0 114 ml O /minute 100 Gm LV when stroke work is maintained constant Thus while rhythm change occurring from PVDs at rest when minute work is constant will not affect MVO_2 in either direction the effect of changing HR may be substantial At constant stroke work the effect of similar HR change becomes approximately five times more pronounced

The above findings were not modified by loss of functioning myocardium resulting from coronary artery occlusion Constancy of MVO at each heart rate step after loss of up to 27 per cent of functional myocardium resulting from coronary occlusion confirms for this range of heart rates the previously reported independence of MVO I from the mass of functioning myocardium It also suggests constancy of efficiency of the intact myocardium for the 14 to 27 per cent range of relative workload increases corresponding to the size of the functionally lost ischemic myocardium for the range of heart rates tested

In conclusion and of possible clinical importance it appears that (1) no significant effect on either MVO or contractility should be expected as the result of rhythm changes devoid of changes in heart rate (2) the effect of heart rate depends to a great extent on the stroke volume Thus changes occurring at constant cardiac output simulating rest are significant but approximately only one fifth of the effect expected at same heart rate and constant stroke volume as may happen during exercise (3) reduction of functioning myocardium by coronary artery ligation does not modify significantly the magnitude direction and quantitative relationship of rate and rhythm effects on MVO_2

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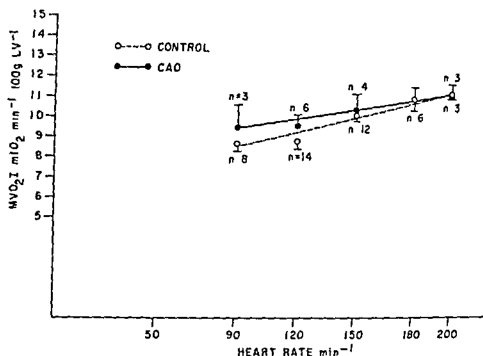


Fig 4 Effect of heart rate on MVO_2I during control and after coronary artery occlusion *(CAO)* Mean values and their standard error are indicated Control and the post CAO data did not differ significantly *MVO_2I* = myocardial O consumption index *n* = number of observations

minute and lowest at HR of 150/minute but no significant slope (Table III) Similarly in both control and post CAO data (Table IV), no significant slope or difference between slopes was demonstrated For constant stroke volume the regression line of LV dp/dt values showed positive slope 10 83 ± 1 3, r = 99, p < 0 05 (Table III) Similar positive slopes of 11 8 ± 1 2 and 11 5 ± 1 5 mm Hg/sec per beat of HR increase respectively (r = 0 99 p < 0 01 and r = 0 98 p < 0 05) were derived in the control and post CAO data of Table IV after normalization for constant SV

CaO_2 pH pO and HCT were kept within normal range and did not vary as a result of rate and rhythm changes The grossly estimated size of ischemic myocardium in the preparations with coronary artery occlusion ranged between 14 and 27 per cent of the wet left ventricular weight

Discussion

In this study with controlled heart rate arterial pressure and cardiac output the effect of number of PVDs on MVO I appeared to be insignificant The mean effect of changing coupling interval of a fixed number of PVDs on MVO_2 appears also to be insignificant although in two out of nine experiments a significant correlation of these variables was found The force-length effect of the post extrasystolic beat shown to increase isometric time tension index by Takeda and colleagues[6] is apparently counterbalanced by the equal decrease of this index associated with the PVD On this basis results of this study concur with previous studies[3,11,1] suggesting that the effect of rhythm changes on contractility if any is negligible

In contrast the significant positive correlation of HR changes with substantial MVO changes was reconfirmed Slopes were approximately five times steeper when in gross simulation of exertion stroke volume was kept constant at all HR steps as compared to those obtained at fixed cardiac output and minute work where in simulation of paroxysmal tachycardias stroke volume and work changed with the reciprocal of heart rate The similarity of corresponding actual and calculated MVO data at fixed SV or CO (Fig 3) suggests that the reciprocal HR to SV relationship is the only factor responsible for this substantial slope difference The findings obtained at constant SV in this study are basically in agreement with previous work in isovolumic left ventricular preparations attributing the effect of heart rate on MVO to changes of contractile state related to the force-frequency relationship[1] In this study at constant CO changes in LV dp/dt (Tables III and IV)

;ase reports

chocardiographic diagnosis of left ventricular nural thrombi occurring in cardiomyopathy

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The diagnosis of left ventricular clots in patients with cardiac disease is often suspected subsequent to an episode of systemic embolization discovered incidentally at the time of left ventriculography or determined at autopsy It has been estimated that emboli originate from within the heart in approximately 80 to 90 per cent of cases [1,2] Since the natural course of these structures is unpredictable earlier diagnosis by simple means may be beneficial in the clinical management of these patients Recently a documented left ventricular thrombus was detected by Echocardiography in a patient with multiple myocardial infarcts This report presents the echocardiographic features of multiple left ventricular thrombi occurring in a patient with congestive cardiomyopathy

Case Report

A 49 year-old black man with a history of chronic alcoholic consumption was admitted to Cook County Hospital on June 20 1976 with progressive exertional dyspnea and vague right sided chest pain of three weeks duration There was no cough fever hemoptysis paroxysmal nocturnal dyspnea peripheral edema or calf pain

Physical examination revealed a chronically ill man The blood pressure was 98/80 pulse 120 beats/minute and respiratory rate 26 breaths/minute The cervical veins were distended at 45 degrees. Bibasilar rales were heard The cardiac impulse was diffuse at the sixth left intercostal space just outside the midclavicular line The first and second heart sounds were normal A third heart sound was noted at the apex No murmurs or rubs were appreciated The liver was enlarged The pulses were normal There was no peripheral edema An initial clinical diagnosis of alcoholic cardiomyopathy was made

The routine admitting laboratory data were normal as was the liver and coagulation studies An electrocardiogram revealed a sinus tachycardia with left anterior hemiblock, poor R wave progressions across the right precordial leads and nonspecific ST wave abnormalities The chest x ray showed moderate cardiomegaly with increased vascular markings.

After two weeks of hospitalization the patient dramatically improved on digoxin diuretics and bed rest Over the next three months his initial symptoms recurred despite alcohol abstention and conventional medical management On September 27 1976 he was rehospitalized markedly dyspneic with hemoptysis bilateral pedal edema and leg pain

Physical examination revealed the patient to be in moderate respiratory distress with a respiratory rate of 28 breaths/minute Blood pressure was 90/"0 pulse was 120 beats/minute and temperature was 99 F There was percussion dullness and râles at the right base The cardiovascular examination was unchanged The liver was enlarged and tender Moderate pedal edema was noted

The pertinent laboratory data showed a prerenal azotemia with marked hepatic and coagulation abnormalities. The electrocardiogram was unchanged A chest x ray again revealed moderate cardiomegaly with a new right lower lobe infiltrate A lung scan suggested the possibility of pulmonary emboli to the right middle lobe

Vigorous treatment for congestive heart failure was insti

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Rece ed f p bli tion Aug 16 1977

Accepted f publicati n Sept. 12 1977

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result in widespread embolization In this regard their earlier identification could be important both diagnostically and therapeutically

Recently Horgan and associates described the echocardiographic features of a documented septal thrombus which occurred in a patient who had sustained several myocardial infarctions The echocardiogram demonstrated a mass of dense echoes which were closely applied to the left septal surface This pattern was similar in appearance to the septal densities described herein The authors also emphasized the impor tance of manually scanning the left ventricle when thrombi are suspected In our case this maneuver was extremely helpful and enabled us to visualize the leading edge of the thrombus (Fig 1 *arrow*) the pitfall of diagnosing a thick ened septum was thus avoided Additionally inferior angulation of the transducer uncovered several smaller apical densities (Fig 2 2B) closely resembling the anatomical findings

The ability to visualize intracavitary thrombi by echocardiography is of course dependent on their size acoustical properties and location In this case the clots were large well organized and within the sound path of the transducer The explanation for the paucity of previous data may therefore relate to the routine omission of the scanning technique the presence of smaller or unorganized thrombi or the appearance of thrombi in atypical locations The inability to identify the smaller right ventricular thrombi and the apicolateral thrombus in this case probably represents a failure to identify these portions of the heart with the conventional single crystal technique Perhaps with the newer wider angle real time imaging systems such areas may be better visualized

We would conclude that recognition of the described echocardiographic patterns may be helpful when the etiology of a systemic embolus is sought or in those patients who are at high risk of developing intracavitary thrombi The sensitivity and specificity of this technique however in detecting such structures is unknown and must await definitive investigation



Fig 3 Pathological specimen of the heart visualizing the large septal thrombus *(1)* the posteromedial thrombus *(2)* with septal bridge *(B)* and apicolateral thrombus *(3)*

Summary

A patient with alcoholic cardiomyopathy presented with recurrent biventricular heart fail ure Echocardiography supported the clinical diagnosis and suggested the presence of multiple left ventricular mural thrombi At postmortem large left ventricular and small right ventricular thrombi were found in association with systemic and pulmonary emboli Echocardiography may be of value in the earlier detection of intramural left ventricular thrombi

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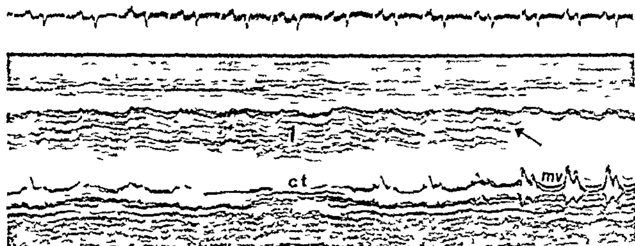


Fig 1 Echocardiogram demonstrating dilatation and hypokinesis of the left ventricle with a cluster of linear densities *(1)* applied to the left septal surface *ct* = chordae tendineae *mt* = mitral valve

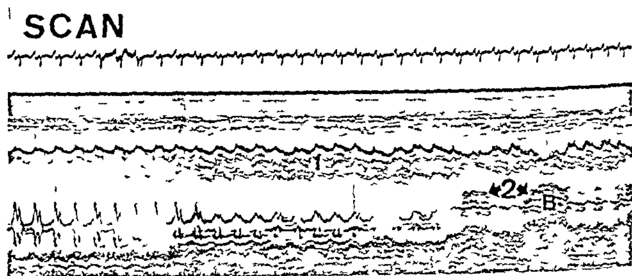


Fig 2 Left ventricular condensed scan showing septal densities *(1)* and additional apical densities *(2)* *B* = apical intracavitary density bridging posterior wall and septum

tuted Anticoagulation was withheld because of the derangement in hepatic and coagulation function studies The patient gradually improved with resolution of hemoptysis and a 30 pound weight loss An echocardiogram (Fig 1) demonstrated dilatation of the left ventricle with hypokinesis and thinning of the posterior wall and septum The left atrium right ventricle and aortic root were of normal dimensions A cluster of linear densities closely applied to the septum (Fig 1 1) was noted at the chordae tendineae level These separated from the septum at the mitral valve level *(arrow)* There was delayed mitral valve closure and reduced leaflet amplitude indicative of an increased end diastolic pressure with diminished mitral valve flow respectively Upon scanning the left ventricle with the transducer additional intracavitary densities (Fig 2 2) were visualized in the area of the apex One such large density (Fig 2 B) appeared to bridge both the septum and posterior wall of the left ventricle Four days thereafter the patient suddenly became apneic and died

Postmortem examination demonstrated the heart to be markedly enlarged weighing 700 Gm The valves were thin and pliable The left ventricle was markedly dilated and lined almost entirely by organized mural thrombi The largest thrombus (Fig 3 1) measured 10 × 7 × 3 cm and was attached to the anteroseptal portion of the chamber A second thrombus (Fig 3 2) located at the posteromedial wall measured 4 5 × 2 5 × 0 4 cm and extended toward the apex At its most inferior portion it bridged the septal thrombus (Fig 3 B) At the apicolateral area another thrombus (Fig 3 3) was observed measuring 6 0 × 3 5 × 2 0 cm Subjacent to the thrombi there was extensive subendocardial fibrosis The right ventricle contained two small mural thrombi in its midportion and one large apical thrombus The coronary arteries were widely patent Pulmonary emboli associated with infarction were noted in the left upper and right lower lobes The right kidney contained an area of infarction There was marked pulmonary congestion

Discussion

Intracardiac mural thrombi are frequently associated with hypocontractile ventricular segments such as occur in myocardial infarction ventricular aneurysm and cardiomyopathy Clinically thrombi may remain dormant or they may

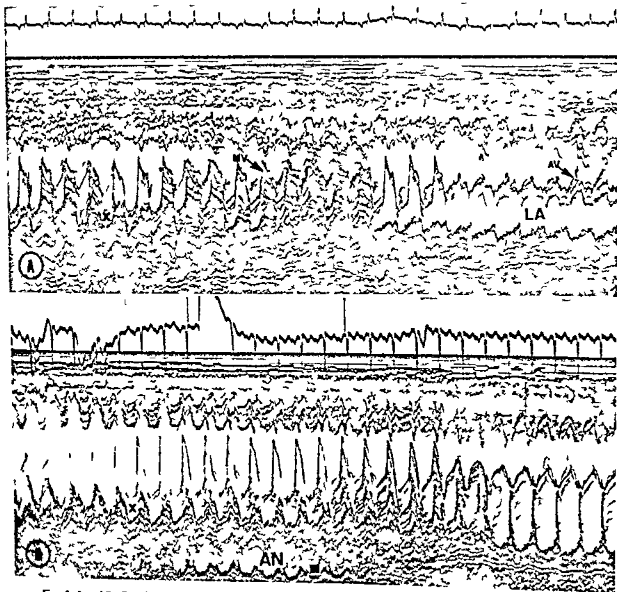


Fig 1 A and B Serial echocardiograms showing A shaggy mitral (MV) densities highly suggestive of vegetations, pansystolic mitral valve prolapse (*) and exaggerated LV posterior wall left atrial junction motion (X) submitrally AV = aortic valve LA = left atrium B further prolapse of the mitral valve leaflets into the left atrium ( ) and the development of a LV echo free space (AN) associated with systolic expansion (■)

An echocardiogram performed on Mar 6 19 6 (Fig 1A) showed pansystolic prolapse of the mitral valve leaflets ( ) associated with shaggy dense material highly suggesti e of vegetations The motion of the left atrial LV junction was exaggerated (X) possibly because of mitral regurgitation The LV and left atrial dimensions were normal

On March ?? the patient had an intermittent pericardial friction rub On March 31 a Grade 3/6 apical holosystolic murmur was noted for the first time The patient continued to run a low grade fever but repeat blood cultures were negative A gallium scan was compatible with multiple areas of muscle abscesses.

A repeat echocardiogram (Fig 1B) revealed a localized echo-free space posterior to the posterior left ventricular wall This echo-free space showed systolic expansion (■) A localized pericardial effusion or a myocardial abscess was considered The posterior mitral valve leaflets were now noted to move briskly anteriorly behind the anterior leaflets and to prolapse into the left atrium during systole (*) suggesting a flail posterior leaflet The previously described shaggy densities were now more granular and localized on the mitral valve

On April 8 19/6 right and left cardiac catheterization was performed (see Table I) Resting right heart and aortic pressures were normal. An aortogram showed no aortic valve or gross coronary artery pathology A right atrial angiogram showed no pericardial effusion but in the levophase there was a poorly defined left ventricular aneurysm

Infective aneurysm of the left ventricle angiographic and echocardiographic features

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An infective (mycotic) saccular aneurysm of the left ventricle (LV) is a rare complication of bacterial endocarditis [1-6]

This paper describes the unique echocardiographic and angiographic features of an infective saccular aneurysm involving the posterior LV free wall subsequent to staphylococcal endocarditis of the mitral valve

To our knowledge the echocardiographic features of such an aneurysm have not been reported

Case report

A 17 year old black male with a known seizure disorder came to the Cook County Hospital emergency room on Feb 25 1976 complaining of generalized myalgias and fever Five days prior to admission he had sustained blunt trauma to the right thigh resulting in persistent pain and swelling There was no history of prior cardiovascular disease rheumatic fever or drug abuse

On admission the patient had a blood pressure of 110/ 0 pulse of 90/minute temperature 102 8 F height 76 inches weight 155 pounds He was lethargic with severe generalized muscle tenderness Cardiac examination revealed a normal heart size and a Grade 2/6 pulmonary flow murmur A chest x ray was normal The electrocardiogram showed non specific ST T changes The white blood count was 8 600/mm Blood cultures grew *Staphylococcus aureus* The C P K was 3 3 0 I.U (Normal 0 to 50 I U)

He was diagnosed as having staphylococcal septicemia and treated with oxacillin and then nafcillin and gentamicin Over the next month the patient showed evidence of septic emboli with Roth spots sub-conjunctival hemorrhages Janeway spots and recurrent crops of cutaneous pustular lesions A muscle biopsy showed acute myositis

Table I Hemodynamic data

	4-8 76	*4 10 76*	*9.6 ?*
Pressures (mm hg)			
RA	1		
RV s/ed	37/1		
PA s/d	30/		
LV s/ed	—	105/9	128 H
Ao s/d	130/100	90/5	122 ?
Cardiac index	2 28 L /min /M²		
Ejection fraction		,0	
Mitral regurgitation		1+	?+

Abbreviations Ao = Aorta d = diastolic pressure ed = end-diastolic pressure LV = left ventricle PA = pulmonary artery RA = right atrial mean pressure RV = right ventricle s = systolic pressure
As seen on LV angiography 0 to 4 + scale

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Received for publication Sept 20 1977
Accepted for publication Oct 25 1977

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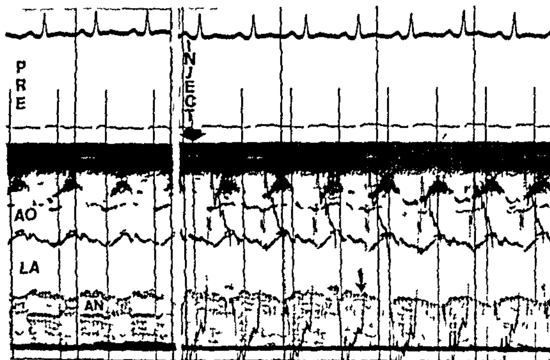


Fig 3 Saline injection into aneurysmal sac at time of cardiac catheterization showing filling of the echo free space *(AN)* *Ao* = aorta *LA* = left atrium *PRE* = prior to saline inj ction.

was no adhesive pericarditis. The mouth of the aneurysm was closed by a Dacron patch and the mitral valve was replaced by a stented porcine aortic valve The postoperative course was unremarkable and the patient had an uneventful recovery

The postoperative echocardiogram (Fig 1C) showed a considerable reduction in the exaggeration motion of the left atrial LV junction *(X)* and obliteration of the previously described echo free space The mitral prosthesis *(MVP)* motion was normal

In September 1976 a murmur of aortic insufficiency was noted for the first time As of June 1978 the patient has remained asymptomatic

Discussion

Mycotic aneurysms of the LV usually involve either the membraneous septum or the mitral-aortic intervalvular fibrosa [8] Unique to our case was the *involvement of the posterior free* wall of the LV

Posterior wall saccular aneurysms having a similar angiographic appearance to that seen in our patient have also been described in young African negroes with idiopathic mitral subannular left ventricular aneurysms [9] but unlike our case they had no underlying infection and probably were of congenital origin

We believe that our patient had a mitral valve ring abscess because he had mitral regurgitation of recent origin and an evanescent pericarditis occurring in the setting of acute staphylococcal endocarditis [9] This mitral valve ring abscess then burrowed into the adjacent myocardium leading to the formation of a LV aneurysm [10]

Sequential echocardiography was diagnostically helpful in this case in the early detection of mitral valve vegetations leading to the development of a flail posterior leaflet along with mitral regurgitation The subsequent formation of a localized posterior echo free space while suggesting either pericardial fluid accumulation or abscess formation favored the latter in light of the patient s clinical course and prior demonstration of vegetations We were able to demonstrate that this echo free space was due to an aneurysmal sac because it could be temporarily obliterated by injecting it with saline at catheterization and also because it could no longer be detected postoperatively The discrepancy in size of the space noted by the angiographic and echocardiographic methods probably represents superior angulation by the single crystal transducer It is anticipated that the development of the newer real time imaging systems will permit broader visualization of these types of structures

Our patient s aneurysm was probably a pseudoaneurysm because (1) the neck of the sac was narrower than its fundus and (2) the surrounding *myocardium* appeared normal and sharply

Fig 1C Serial echocardiogram showing obliteration of the echo free space postoperatively and a normally functioning mitral valve prosthesis *(MVP) LA* = left atrium



Fig 2 LV angiogram during systole in 30 degree right anterior oblique view showing a saccular aneurysm of the posterior wall *(outlined by black arrows)* associated with prolapse of posterior mitral valve leaflet (*)

In order to better define the LV aneurysm left heart catheterization was performed The LV pressures were normal (Table I) Left ventriculography performed in 30 degree right anterior oblique and 60 degree left anterior oblique views showed a postero basal aneurysm arising at the level of the mitral valve ring as well as mild *mitral regurgitation* with mitral prolapse (Fig 2) There was no venticular septal defect

In May 1976 the patient developed progressive obstructive jaundice and hepatomegaly Celiac angiography revealed multiple mycotic aneurysms of the hepatic artery compressing the common bile duct Ligation and drainage of the pseudo-aneurysm of the hepatic artery was accomplished without sequelae

Further details concerning this patient s hepatic artery aneurysm have recently been published by Mojab and associates (Am J Roentgenol 128 143 144 1977)

A follow up left ventriculogram in August 1976 showed progressive enlargement of LV aneurysm with an increased left ventricular end diastolic pressure *(Table I)* Saline injection of the aneurysm with simultaneous echocardiography obliterated the previously described posterior echo-free space (Fig 3) thus providing supportive evidence that the echo free space represented the aneurysmal sac

On August 31 1976 the patient underwent cardiac surgery At operation a saccular aneurysm of LV was found The aneurysm was 2 cm wide 10 cm long and 0 2 cm thick with an approximate volume of 50 c c It was located in the posterobasal aspect of free wall of LV just below the mitral valve and inferior to the circumflex artery The aneurysm appeared to be endothelialized covered by epicardium and contained no blood clots No microscopic sectioning of the wall of the aneurysm was carried out There was no involvement of the membraneous septum or the aorto mitral intervalvular fibrosa by the aneurysm There was a perforation 1 cm in diameter of both mitral valve cusps at their posterior commissural junction The aortic valve was not visualized There however no aortic regurgitation was seen at operation.

Spironolactone

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The isolation and identification of aldosterone was followed by attempts to synthesize spirolactone steroids capable of blocking its physiologic and pharmacologic effects The most important and effective aldosterone antagonists are spironolactone canrenone canrenoate and more recently prorenoate The spironolactones were the first potassium sparing diuretics and have been increasingly used for the clinical treatment of congestive heart failure hepatic ascites primary aldosteronism and essential hypertension [32]

Chemical properties and methods of quantitation

Spirolactones have a structure similar to that of other steroids with a lactone ring as a substituent at C 17 (Fig 1) Spironolactone and its metabolites are usually designated by Roman numerals in the chemical and pharmacologic literature Spironolactone is the active constituent of Aldactone whereas canrenoate is a water soluble potassium salt used for intravenous injection (Fig 1) When canrenoate is reconstituted from its lyophilized form prior to injection the solution often becomes turbid after a short period of standing at room temperature The turbidity appears to be due to precipitation of canrenone (aldadiene SC 9376) a pharmacologically active derivative of canrenoate Thus canrenone can be formed from canrenoate both *in vitro* and *in vivo* It is not established whether the turbid solutions are clinically effective when injected intravenously

Several methods are available for quantitation of spironolactone and its metabolites in body fluids These include radioactive tracer techniques chromatography fluorescence mass spectrometry and ultraviolet spectrometry [1 39] A radioimmunoassay will soon be available [40] One disadvantage of techniques based on quantitation of tritiated spironolactone is that relatively large amounts of tritiated water are formed by endogenous metabolism of the parent compound [41]

Using spectrophotofluorometric technique for quantitation of canrenone Karim and colleagues [2] were able to assay this compound in a 1 ml plasma sample at levels as low as 15 ng /ml The coefficient of variation for identical samples in the range of 75 to 1 200 ng /ml was 8 per cent or less Sadee and associates[3] modified the technique to allow separate quantitation of spironolactone canrenoate and the polar glucuronic ester conjugate of canrenoate The method is sensitive and specific enough to allow reliable measurement of these compounds in plasma after therapeutic doses of spironolactone

The presence of spironolactone and its metabolites in plasma appears to interfere with determination of plasma cortisol by fluorometric assay [3 47] It is also suggested that spironolactone metabolites interfere with estimation of serum digoxin by radioimmunoassay [51]

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Supported in part by Deutsch F rsch ngsgem nsch ft, Bo n B d Godesberg West Germ y and by Grants MH 1?2?9 d HL-18003 from the United St tes Public H lth Servic

Received f public tion Feb 10, 1977

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demarcated from the mouth of the sac The absence of both an adhesive pericarditis and a thrombus within the sac may be because the pseudoaneurysm was not as longstanding as those reported in the literature [11 18]

In conclusion, this case report emphasizes that an infective aneurysm of the LV should be suspected if echocardiography shows a localized echo free space in a patient with staphylococcal septicemia An early diagnosis by LV angiography is essential since an infective aneurysm has a significant risk of rupture[1] and may be surgically treatable

Summary

A 17 year old man with staphylococcal endocarditis of the mitral valve developed an infective aneurysm of the posterior left ventricular wall Echocardiography revealed an echo free space posterior to the posterior left ventricular wall This echo free space undoubtedly represented the aneurysmal sac, because it could be temporarily obliterated by injecting saline into it and was no longer detectable following surgical closure of the sac Thus echocardiography may be helpful in the detection of an infective aneurysm of the left ventricle

We gratefully acknowledge the secretarial assistance of Mrs Evelyn Hunt and the technical assistance of Mr R Fischer Mrs Dorothy Gore Mrs S Rochon and Miss M Smith

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intravenous canrenoate in equimolar doses has been used as an absolute bioavailability standard

After oral administration of a solution of canrenoate the serum concentration curve was nearly superimposable upon that obtained after intravenous injection suggesting that canrenoate is rapidly and completely absorbed from an oral solution and that a clinically important first pass effect does not exist[5] Bioavailability of spironolactone tablets reached 96 per cent in comparison to an oral solution but only 60 per cent when compared with oral administration of canrenoate K in one patient[5] In a more extensive crossover study in 12 healthy volunteers[6] bioavailability of conventional 25 mg spironolactone tablets was compared to that of a new 100 mg tablet formulation and to an oral solution The mean (±S D) bioavailability of the two tablets relative to the oral solution based upon the area under the 24 hour canrenone plasma concentration curve were 99 6 ± 18 2 per cent and 92 1 ± 22 9 per cent Differences in the peak plasma concentrations of metabolites among two tablet preparations (25 and 100 mg) of spironolactone were unimportant[60] Sponer and colleagues[6] investigated the absolute and relative bioavailability of two oral spironolactone preparations in 20 volunteers Absorption of 100 mg of spironolactone given either as two tablets or one capsule was complete However when 400 mg were given orally as a single dose absorption of the drug was reduced

Metabolic pathways As indicated previously the metabolic degradation of spironolactone in humans proceeds very rapidly by enzymatic cleavage of the C 7 acetylthio substituent to yield canrenone Serum concentrations of spironolactone fall to undetectable limits within a few minutes of a dose The two major metabolites canrenone and canrenoate exist in equilibrium[5]

Comparison of fluorescent compounds and metabolites in serum and urine with the findings from studies of radioactive labeled spironolactone and canrenoate clearly demonstrate the formation of a variety of nonfluorescent radioactive metabolites including tritiated water After administration of tritiated canrenoate *elimination* of total radioactivity proceeds with a much slower half life (43 to 70 5 hours) than does elimination of fluorescent substances due to the presence of nonspecific radioactivity Karim and colleagues[31] suggest that the apparent elimination half life of total radioactivity extractable into ethyl acetate (about 37 hours) probably represents that attributable to spirolactones In any case accumulation of these nonfluorescent and as yet unidentified metabolites may explain in part why maximal clinical effects of spironolactone are achieved only after several days of treatment and that efficacy of the drug can still be demonstrated 2 to 3 days after the last dose Since the activity of single doses of spironolactone persist for up to 24 hours[62] once or twice daily dosage with spironolactone may be satisfactory

Karim and co workers[35] described the disappearance of serum radioactivity following intravenous tritiated canrenoate by a triexponential function The terminal elimination portion of the curve was reached after 5 hours Forty seven per cent of radioactivity was excreted in the urine and 14 *per cent in the feces* within 5 days Approximately 50 per cent of radioactive compounds were fluorescent metabolites Only 1 per cent of the dose was excreted in the urine as unchanged drug One of the major water soluble metabolites was a glucuronide ester[35] After oral administration of tritiated spironolactone in an alcoholic solution no unchanged spironolactone was recovered in the urine In 5 days 32 per cent of radioactivity was excreted in urine and 23 per cent in feces The major urinary metabolites were canrenone (5 per cent of the dose) the 6β hydroxy sulfoxide metabolite (5 per cent) and the glucuronide ester of canrenone (6 per cent) When potassium canrenoate was administered intravenously 3 4 per cent of the dose was excreted in the urine as unchanged canrenone Further study of human metabolites of spironolactone is needed since *metabolites* other than canrenone and canrenoate may contribute to its clinical activity[6, 65] Structure activity studies of spironolactone analogues suggest that beta unsaturation at the C6/C7 position gamma lactone unsaturation and gamma lactone ring opening with formation of a water soluble salt all result in decreased activity[66]

Both spironolactone and canrenone are extensively bound to plasma proteins (89 per cent or more) at therapeutic concentrations[67] Blood to

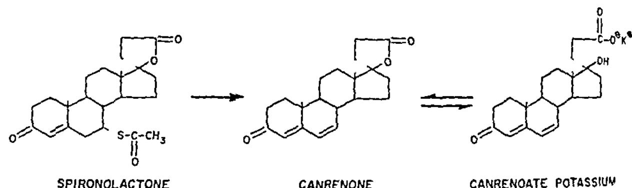


Fig 1 Structural formula of spironolactone and its major metabolites canrenone (aldadiene) and canrenoate (shown as the potassium salt)

Pharmacokinetics

Animal studies Following intravenous administration of spironolactone to dogs or rats[37, 5, 53] the apparent elimination half life of the parent drug is approximately 10 minutes Excretion of radioactive labeled spironolactone and canrenoate occurs mostly via the biliary tract in the form of polar conjugated metabolites (80 to 95 per cent within 12 hours in the rat, 35 per cent during 6 hours in the dog) Renal excretion of radioactivity reaches only 3 per cent over 12 hours in the rat and 1 per cent within 6 hours in the dog Bioavailability studies in the dog indicate that absorption of spironolactone is about 80 per cent complete A suitable pharmacokinetic model for spironolactone in these species has not yet been developed

Clinical Studies

Distribution elimination and accumulation Spironolactone itself is very rapidly cleared by the human organism The metabolites canrenone and/or canrenoate, having considerably longer half life values than the parent drug are usually measured in body fluids after administration of spironolactone to humans The apparent elimination half life of canrenoate plus canrenone was between 17 and 22 hours after a single intravenous injection of canrenoate to five patients[54] Karim and co workers[41] in a study of five healthy male subjects similarly observed a mean elimination half life of 16 8 hours for these two compounds after single doses of spironolactone After termination of chronic spironolactone therapy (200 mg once daily) the apparent elimination half life of canrenone averaged 19 7 hours, however, when the same total dose was divided into 50 mg taken 4 times daily the apparent elimination half life was 12 5 hours[55] With both dosage regimens steady state was achieved after about 4 days of therapy, although the amount of interdose fluctuation in plasma levels on the 'q i d' regimen was less than on the once-daily schedule The clinical significance of these fluctuations is not known[55]

In another multiple dose study, 100 mg of oral spironolactone was administered twice a day to six patients recovering from acute myocardial infarction[56] Accumulation of canrenone and canrenoate was only 50 per cent complete after one to four days The apparent elimination half life values observed after both single doses and 10 days of chronic administration were not significantly different being about 20 hours in both instances (range 17 to 22 hours) The amount of time necessary for achievement of steady state was longer than that predicted on the basis of single dose studies Thus elimination and accumulation half lives are not consistent The reasons for this are not established, although the authors suggest a change in macromolecular binding or tissue distribution due to cumulation of unknown metabolites[56]

During three weeks of spironolactone therapy in 44 patients steady state plasma levels of canrenone were no different in patients with impaired renal or hepatic function than in individuals without such diseases[56] Steady state plasma levels differed fifteenfold among individuals receiving the same daily dose Higher maintenance doses led to approximately proportional increases in steady state plasma levels

Biologic availability Problems with bioavailability of spironolactone preparations have been observed since as early as 1962[57, 58] A parenteral preparation of spironolactone for use in absolute bioavailability studies is not available[59] Instead

-travenous canrenoate in equimolar doses has en used as an absolute bioavailability standard

After oral administration of a solution of canrenoate the serum concentration curve was nearly superimposable upon that obtained after intravenous injection suggesting that canrenoate is rapidly and completely absorbed from an oral solution and that a clinically important first pass effect does not exist[5] Bioavailability of spironolactone tablets reached 96 per cent in comparison to an oral solution but only 60 per cent when compared with oral administration of canrenoate K in one patient In a more extensive crossover study in 12 healthy volunteers[6] bioavailability of conventional 25 mg spironolactone tablets was compared to that of a new 100 mg tablet formulation and to an oral solution The mean (±S D) bioavailability of the two tablets relative to the oral solution based upon the area under the 24 hour canrenone plasma concentration curve were 99 6 ± 18 2 per cent and 92 1 ± 22 9 per cent Differences in the peak plasma concentrations of metabolites among two tablet preparations (25 and 100 mg) of spironolactone were unimportant Sponer and colleagues investigated the absolute and relative bioavailability of two oral spironolactone preparations in 20 volunteers Absorption of 100 mg of spironolactone given either as two tablets or one capsule was complete However when 400 mg were given orally as a single dose absorption of the drug was reduced

Metabolic pathways As indicated previously the metabolic degradation of spironolactone in humans proceeds very rapidly by enzymatic cleavage of the C 7 acetylthio substituent to yield canrenone Serum concentrations of spironolactone fall to undetectable limits within a few minutes of a dose The two major metabolites canrenone and canrenoate exist in equilibrium[3, 5]

Comparison of fluorescent compounds and metabolites in serum and urine with the findings from studies of radioactive labeled spironolactone and canrenoate clearly demonstrate the formation of a variety of nonfluorescent radioactive metabolites including tritiated water After administration of tritiated canrenoate elimination of *total* radioactivity proceeds with a much slower half life (43 to 70 5 hours) than does elimination of fluorescent substances due to the presence of nonspecific radioactivity Karim and colleagues[1] suggest that the apparent elimination half life of total radioactivity extractable into ethyl acetate (about 37 hours) probably represents that attributable to spirolactones In any case accumulation of these nonfluorescent and as yet unidentified metabolites may explain in part why maximal clinical effects of spironolactone are achieved only after several days of treatment and that efficacy of the drug can still be demonstrated 2 to 3 days after the last dose Since the activity of single doses of spironolactone persist for up to 24 hours[6] once or twice daily dosage with spironolactone may be satisfactory

Karim and co workers[35] described the disappearance of serum radioactivity following intravenous tritiated canrenoate by a triexponential function The terminal elimination portion of the curve was reached after 5 hours Forty seven per cent of radioactivity was excreted in the urine and 14 *per cent in the feces* within 5 days Approximately 50 per cent of radioactive compounds were fluorescent metabolites Only 1 per cent of the dose was excreted in the urine as unchanged drug One of the major water soluble metabolites was a glucuronide ester[35] After oral administration of tritiated spironolactone in an *alcoholic solution* no unchanged spironolactone was recovered in the urine In 5 days 32 per cent of radioactivity was excreted in urine and 23 per *cent in feces* The major urinary metabolites were canrenone (5 per cent of the dose) the 6β hydroxy sulfoxide metabolite (5 per cent) and the glucuronide ester of canrenone (6 per cent) When potassium canrenoate was administered intravenously 3 4 per cent of the dose was *excreted* in the urine as unchanged canrenone Further study of human metabolites of spironolactone is needed since metabolites other than canrenone and canrenoate may contribute to its clinical activity[6, 65] Structure activity studies of spironolactone analogues suggest that beta unsaturation at the C6/C7 position gamma lactone unsaturation and gamma lactone ring opening with formation of a water soluble salt all result in decreased activity[66]

Both spironolactone and canrenone are extensively bound to plasma proteins (89 per cent or more) at therapeutic concentrations[6] Blood to

plasma concentration ratios are about 0.5, suggesting no selective uptake of the compounds by red cells.

Drug distribution and pharmacologic effects. In rats the maximal reduction of aldosterone-induced sodium retention occurs when renal elimination of spironolactone is maximal.[68] Thus the extent of the tubular effects of the anti-aldosterones appears to depend on their concentration in the renal tubules. Clearance studies[1] indicate that spironolactone is secreted by the tubules. This secretion can be blocked with bromcresol green, with a parallel decline in renal effects. *In vitro,* 11-hydroxy spironolactone inhibits the synthesis of aldosterone in rat adrenals.[6] *In vivo* the drug stimulates the renin-angiotensin-aldosterone system to a great extent with hyperplasia of the zona glomerulosa of the adrenals.[30] Spironolactone induces hyperreninemia, hyponatremia, and hyperkalemia which again stimulates the secretion of aldosterone.[9] This effect of increased aldosterone secretion after high doses of 800 to 2 000 mg per day of spironolactone has been applied clinically for treatment of the post-traumatic edema of the brain.[1]

Mechanisms of action

Spironolactone is a competitive antagonist of aldosterone and modifies electrolyte metabolism only in the presence of aldosterone-like compounds.[78] It reverses all electrolyte-regulating effects of aldosterone regardless of the tissue studied. The effects of spironolactone are surmountable by raising the level of aldosterone-like compounds.[8, 9] Spironolactone inhibits the formation of the aldosterone complex in the nuclei of kidney epithelial cells of adrenalectomized rats. This occurs at concentration ratios that inhibit the action of aldosterone in the rat *in vivo*.[80] Recent studies in humans suggest a direct inhibitory effect of canrenone on adrenal aldosterone production.[1]

In vitro studies with kidney tissue slices from rats demonstrate displacement of aldosterone from its specific intracellular receptors by spironolactone.[6]

Influence on myocardial contractility

Positive inotropic effects of the spirolactones have been demonstrated *in vitro* and *in vivo* in humans during cardiac catheterization.[8, 88] The injection of 200 to 400 mg of canrenoate in 40 patients resulted in a long lasting increase of stroke volume as well as an increase in the maximal slope of the pressure-time curve in both ventricles. These positive inotropic effects could also be demonstrated in digitalized patients, and therefore are additive to the effects of digitalis. Improvement in cardiac contractility has been observed during long term spironolactone therapy as well.[5] The mechanism of this action is not well understood but spironolactone does inhibit sodium-potassium ATPase in human erythrocytes, similar to that produced by cardiac glycosides.[89]

Effects on respiration

Respiratory improvement has been observed in patients with chronic respiratory insufficiency after administration of spironolactone.[90, 97] Although progesterone, a structurally related steroid, produces direct respiratory stimulation, this has not been shown with spironolactone.[98] Canrenoate does not change the response to a carbon dioxide challenge.[99] Spironolactone lowers neither airway resistance nor pulmonary compliance.

Antiandrogenic effects

Erbler[100] demonstrated a clear decline in plasma testosterone levels over 9 hours after a single dose of 5 mg/Kg of canrenone to healthy males. Stripp and associates[101] administered 400 mg of spironolactone daily to five healthy male volunteers for 5 days. Plasma progesterone and 17α-hydroxy progesterone increased significantly. Plasma follicle stimulating hormone and luteinizing hormone levels also increased but the effect was only transient and was not significant by the third and fifth days of the study. Plasma testosterone, 17β-estradiol and prolactin did not change significantly. However, the first plasma sample was not taken until 12 hours after the initial dose at which time Erbler[100] found that testosterone levels were returning to normal.

Studies in rats suggest that spironolactone blocks testosterone receptors.[10, 103] Castro and co-workers[104] attempted to use spironolactone therapeutically for hypertrophy of the prostate but obtained only temporary improvement of symptoms. Unwanted antiandrogenic effects

mmonly accompany spironolactone therapy id are discussed in the section on side effects

rug interactions

Antagonism by salicylates In 1962 Elliott[105] suggested a possible antagonism of spironolactone's natriuretic effect when it was given with aspirin This was later documented in laboratory animals and in man[106 08] Sodium excretion during long term treatment with spironolactone (100 mg per day) was reduced by one third when 600 mg aspirin was coadministered [08] In another study [9] aspirin coadministration reduced urinary excretion of canrenone between 4 and 6 hours after ingestion of spironolactone Such findings suggest that aspirin and spironolactone should not be coadministered if possible A similar interaction was demonstrated for sodium salicylate indomethacin and mefenamic acid but not for the analgesic antipyretic drug acetaminophen In rats however indomethacin did not antagonize spironolactone's effect on the kidney[110] Steiness demonstrated reduction in the renal tubular secretion and clearance of digoxin by spironolactone although the magnitude of the effect was small

Enzyme induction and inhibition The influence of spironolactone on microsomal enzyme activity and the pharmacokinetics of coadministered drugs has been investigated extensively in various animal species and in man [1 6] (Table I) In humans simultaneous administration of 400 mg of spironolactone shortens the half life of digitoxin by 20 per cent Urinary excretion of unchanged digitoxin decreases from 80 to 66 per cent with an increase of water soluble metabolites from 12 to 26 per cent The profound effects of spironolactone upon pharmacokinetics of methyldigoxin observed in rats are without any significance for human conditions Antipyrine half life was shortened in nine volunteers from 12 4 to 7 6 hours after a 2 week period of spironolactone treatment In animal studies the enhanced catabolism of many drugs by spironolactone has been successfully applied to prevent or reduce toxicity by these drugs (Table I) For other substances (such as mercury furosemide and digitalis) the exact mechanism by which spironolactone prevents toxicity in animals is not known Some studies demonstrate inhibition of enzyme activity by spironolactone[19 1 2 163 4] Microsomal cytochrome P 450 activity in the guinea pig and the dog was reduced 50 to 80 per cent by spironolactone administration with a simultaneous increase in 17α hydroxylase activity Spironolactone inhibits corticosterone production in quartered rat adrenals

Table I Effects of spironolactone on hepatic function

Species	Effect	Reference
Rat	Increased bile flow	11? 115
	Increased liver weight	116
	Increased activity and/or quantity of liver enzymes	
	bilirubin UDP glucuronyl transferase	112 114
	ethylmorphine N demethylase	117 119
	aniline hydroxylase	118 120
	cytochrome C reductase	116 117
	3 4 benzpyrene hydroxylase (in females)	117
	Accelerated biotransformation or elimination of	
	aniline	121
	bilirubin	114
	benzo (a)pyrine	116
	pentobarbital	1?2 1?3
	hexobarbital	117 1?1
	bromsulphthalein	113
	phenol 3 6-dibromophthalein disulfonate	113
	dimethylbenzanthracene	1?4
	bishydroxycoumarin	125
	3 4 benzpyrene	116
	diazepam	115
	spironolactone	117 126
	digitalis glycosides	119 127 137
Mouse	Increased liver weight	119 127
	Increased activity of liver enzymes	
	ethylmorphine N demethylase	119
	NADPH oxidase	119
	cytochrome P 450	119
	NADPH cytochrome C reductase	117
	NADPH-cytochrome P-450 reductase	119
	Accelerated hexobarbital metabolism	138
Man	Accelerated biotransformation of digitoxin	139
	Accelerated biotransformation of antipyrine	140-142

Biotransformation stimulated in females impaired in males

although the effect of canrenone is considerably greater[164]

Antihypertensive effects

Spironolactone produces very little fall in blood pressure in normotensive subjects Until the early 1960s the blood pressure lowering effect of spironolactone in hypertensive patients was not considered to be attributable to a decrease of circulatory volume[8,10] Recently however, it has been shown that even in patients with primary hyperaldosteronism the antihypertensive action of spironolactone is nonspecific and largely dependent on depletion of salt and water[165] Furthermore, maintenance of reduced plasma volume or extracellular fluid volume is essential for continued antihypertensive activity of spironolactone This contrasts with earlier findings demonstrating that blood pressure is reduced either by spironolactone or thiazide diuretics in essential hypertensives, whereas patients with primary aldosteronism respond only to spironolactone[11,1] It now appears questionable whether high dose spironolactone is the treatment of choice in primary aldosteronism Brown and associates[11] compared the results of spironolactone therapy and ablative surgery in 67 patients with elevated aldosterone serum levels They confirmed and extended earlier reports of the predictive value of spironolactone on the subsequent hypotensive effect of adrenal surgery in patients with adrenocortical adenoma[1,6] On the other hand occasional failure to respond to spironolactone and subsequently successful surgery have been reported[7,11,13] The situation however might be different in cases with carcinoma or micronodular hyperplasia of the adrenal glands[167] For the latter it has been stated that no fall in blood pressure can be expected after surgical intervention if a 4 week therapeutic trial with spironolactone is unsuccessful[168] Thus spironolactone may be a reasonable therapeutic alternative for patients with adrenocortical adenoma who are not candidates for surgery

Patients with essential hypertension can be divided into those with low low normal normal and high plasma renin activity (PRA)[3,16,171] Whereas spironolactone does not appear to be very effective in hypertensive patients with normal or elevated PRA, the drug reduces the blood pressure in about 75 per cent of patients with hyporesponsive PRA[2,3,171] A better blood pressure response in this group of patients has also been demonstrated for hydrochlorothiazide however despite comparable diuretic response the hypotensive response observed with spironolactone was significantly greater suggesting that mineralocorticoid excess may be responsible for the hypertension and low PRA[1] On the other hand, two reports suggest a similar antihypertensive effect for spironolactone and chlorthalidone with both drugs having similar effects on PRA and plasma volume[1,173] A third study demonstrated that chlorthalidone spironolactone and propranolol had similarly effective antihypertensive properties in patients with essential hypertension and normal PRA[174]

The value of classification of patients with essential hypertension according to PRA is not established Spironolactone interferes with the PRA even up to 9 months after discontinuation of the drug[175] Although aldosterone secretion rates are higher in secondary rather than in primary aldosteronism, spironolactone has little or no effect on the arterial pressure in secondary aldosteronism

Clinical use as a diuretic

Spironolactone is an effective diuretic agent in patients with edema or ascites from heart failure cirrhosis or renal impairment and does not directly influence renal blood flow or glomerular filtration rate[15,9] Whereas hepatic coma can be precipitated by treatment with thiazide diuretics, perhaps as a result of potassium depletion this risk is lessened when spironolactone is used Since aldosterone secretion is not raised in untreated congestive heart failure the success of spironolactone treatment will be more evident when aldosterone secretion has been provoked by sodium depletion resulting from long term therapy with other diuretics Spironolactone is often useful as a diuretic in patients with edema due to the nephrotic syndrome who have not responded to thiazide treatment and bed rest alone[1,4]

Electrolyte balance

Aldosterone antagonists block sodium reabsorption in the distal nephron whereas most of the other diuretics prevent sodium reabsorption proximally Thus additional blockade of sodium reabsorption might be obtained by combining other diuretics with spironolactone Ammonium and hydrogen ion excretion is decreased by

spironolactone [9] Since the drug decreases sodium absorption in the distal tubule the ability to excrete dilute urine is impaired and hyponatremia can be a consequence of therapy

Spironolactone blocks aldosterone dependent potassium excretion This is therapeutically useful since most patients with edema treated with other diuretics experience potassium depletion It has been suggested that greater sodium diuresis will occur if potassium supplements are given during combined therapy with spironolactone and thiazide diuretics [180] However coadministration of potassium supplements and spironolactone should be undertaken only with great caution due to the risk of hyperkalemia Spironolactone likewise impairs magnesium excretion The clearance of magnesium is reduced by spironolactone while the magnesium to potassium clearance ratio is unchanged [18]

Wills and associates [82] have shown that spironolactone in a dose as low as 200 mg daily increases urinary calcium excretion However Prati and colleagues[183] demonstrated that hypercalciuria after spironolactone administration is an artifact due to the calcium content (approximately 37 mg) of commercially available spironolactone tablets

Unwanted effects

A report from the Boston Collaborative Drug Surveillance Program indicated that 788 (5 9 per cent) of 13 349 hospitalized medical patients received spironolactone during their hospital stay Unwanted side effects were attributed to spironolactone in 164 (20 8 per cent) of these patients These adverse effects included hyperkalemia (41 5 per cent of adverse reactions) dehydration (16 5 per cent) hyponatremia (11 5 per cent) gastrointestinal symptoms (11 percent) neurologic complaints (9 8 per cent) exanthema (2 4 per cent) and gynecomastia (1 2 per cent) Some of the unwanted effects i e hyperkalemia hyponatremia hypovolemia might have been avoided if the drug were administered more cautiously Hyperkalemia clearly is the most important and serious potential complication of spironolactone therapy The risk is greater in patients with renal insufficiency and those who receive potassium supplements In rare cases hyperkalemia might contribute or lead to intermittent paralysis

Because of its steroid configuration spironolactone has endocrine effects which are not easily explained by a single mechanism [90, 102, 8, 190, 94] In male patients gynecomastia impotence and diminished libido have been reported with doses as low as 100 mg per day In women reversible oligomenorrhea amenorrhea and breast soreness have been noticed Loube and Quirk[19] observed five women in whom breast carcinoma developed during or after the prolonged administration of spironolactone The number of cases however is too small to draw any conclusions and the findings may well be purely coincidental

New spirolactones

Prorenoate is a water soluble salt of a steroid acid structurally related to spironolactone [198, 199] The potency of prorenoate in man with respect to spironolactone as measured by retention of potassium (3 8 1) is significantly higher than its relative potency in promoting natriuresis (1 6 1) [198] In a single dose study the responses to prorenoate potassium 40 mg were not different from those to spironolactone 100 mg [200] The possible clinical role of prorenoate is now under evaluation

We are grateful for the editorial assistance of Ms Ann Werner

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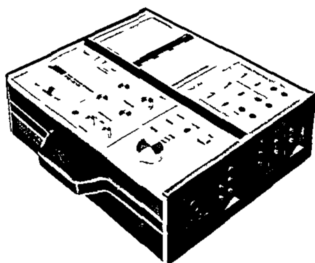
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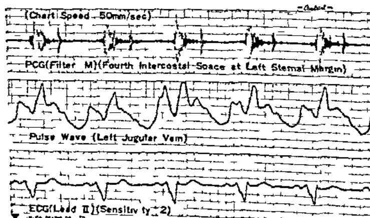
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Diabetic angiopathy—its lessons in vascular physiology

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Many of the diabetic s cardiovascular problems differ from those of the non diabetic only by occurring more often What has been learned by the cardiologist is equally applicable to the problems of these diabetics There are however some conditions and complications unique to the diabetic which are not regularly seen by the cardiologist Many of these sequelae are due to vascular alterations specific to diabetes The endocrinologist s improving understanding of this diabetic *angiopathy* has produced some points of interest for cardiologists which are discussed here

The concept of diabetic angiopathy

In the 19th century ketosis prone diabetics usually survived for only a brief period Changes observed at autopsy were almost all caused by marked hyperglycemia Only diabetics with onset in middle and later life survived long enough to have cardiovascular neurologic and ophthalmologic difficulties[1] The only cardiovascular complication regularly linked to chronic diabetes was gangrene of the lower extremities[2] The use of insulin for treating young diabetics has demonstrated that diabetics of all ages are subject to specific changes in these three systems

Systematic analysis of diabetics surviving for more than 15 years demonstrated that many specific long term complications of diabetes were mediated by a disturbance of the circulation Diabetic retinopathy neuropathy and nephropathy are now often merged under the collective term diabetic angiopathy Because most of the vessels affected are small we often add the prefix micro to angiopathy The local pathology is different in the eye kidney and nervous system But in all three areas it develops as duration increases In each area changes develop in parallel with those elsewhere

The term diabetic angiopathy should be used only for conditions specific to the diabetic state not for changes secondary to atherosclerosis occurring in the diabetic Calcific changes in the arterial media illustrate this distinction quite well Their occurrence is more closely related to duration of diabetes than to age[5] but symptoms are more likely to be age related The arterial media changes interact with arterial intima changes to produce a rather profound disturbance of the peripheral circulation in older diabetics It may be impossible in an individual patient with peripheral vascular insufficiency to say how much is due to diabetic angiopathy and how much to atherosclerosis[6] Calcium in the arterial media favors a role for diabetic angiopathy since calcification is associated with changes in elastin[7] and with PAS positivity in the media Similar histologic changes without calcification are found in a wide variety of vessels in the diabetic—arteries arterioles capillaries venules and veins[8] The pathology in the arterial system shares features with changes found in hypertension[9] The slow development of widespread vascular changes is the most substantial evidence for the concept of diabetic angiopathy

Angiopathy and atherosclerosis

Some writers consider that diabetic small vessel changes develop in parallel with atherosclerosis in

From the Sansum Medical Rese rch F u d tio Santa B rb ra Calif

Supported in part by th Doris F y Palm Tru t nd the Kroc Foundation

Recei ed for public tion Apr 11 19"8.

Reprint requests Don ld E. M M llan M D S m Medical Research Found tion, P O Drawer LL, Santa B rb a C lif 93102.

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larger arteries This concept should not be accepted since it is contradicted by a number of studies The Pima Indians of Arizona are regularly obese Half of them develop diabetes in maturity They have much less ischemic heart and peripheral artery disease than in the general U S population, but the diabetic Pimas have just as much retinopathy and nephropathy [10] In parts of the world where diabetes and malnutrition coincide, there is also as much retinopathy but much less atherosclerosis [11] The association we make between atherosclerosis and diabetes is probably attributable to two factors First the majority of diabetes is probably attributable to two factors First, the majority of diabetics in western society have maturity onset non ketosis prone diabetes, a condition provoked by overweight Since these diabetics are usually obese they would be expected to have more atherosclerosis [12] Second, the development of hyperglycemia is accompanied by elevation of the plasma triglyceride level Triglyceride's role in the generation of atherosclerosis in the non diabetic is only marginal but its elevation is linked quite distinctly to atherosclerosis in diabetics [13]

Angiopathy and hypertension

Diabetics are more likely to be hypertensive than non diabetics [14] Even at diagnosis there is often a mild increase in blood pressure This may be attributable to a tendency of the blood volume to be expanded a process which may be associated with low aldosterone levels [15] The combination of diabetes and hypertension is worse than either disorder alone Diabetic microangiopathy and hypertension share pathologic features in the arterioles, even though diabetic arteriolar changes are patchier than those in hypertension Diabetes involves mainly arterioles small enough to lack an internal elastic lamina, while hypertension affects somewhat larger arterioles just as strikingly [16] The hyaline arteriolosclerosis in the eye and kidney in benign hypertension and in diabetic retinopathy and nephropathy are therefore rather similar [16, 17] Hypertension accompanying diabetic nephropathy accelerates the progression of uremia [18] The overlapping anatomic changes in hypertension and diabetes appear to be additive

Angiopathy and basement membrane changes

The ability to look at smaller and smaller structures with the electron microscope has changed our concept of diabetic angiopathy The smallest microcirculatory structure the capillary, has been found to have a thickened basement membrane in diabetes Controversy about the role of capillary basement membrane thickening in *causing* diabetes has provoked much interest During the basement membrane controversies we have often forgotten much that we knew before about how angiopathy develops and progresses Capillary basement membrane thickening in diabetes is widespread in the body [19] but most studies have concentrated on three body tissues—skeletal muscle, the kidney, and the eye Skin was found to have too erratic an anatomy to be used

Studies of skeletal muscle capillary basement membrane are the most widely known source of major controversy Zacks and associates[20] first established that it is thickened in diabetes Siperstein and colleagues[19, 1] used this observation as a means for investigating large numbers of diabetics Their studies were started when interest in a 'pre diabetic' state was widespread Diabetes was assumed to be inherited as a recessive trait with incomplete penetrance Studies on individuals who had close family members with diabetes showed basement membrane thickening in the presence of a normal glucose tolerance Although the thickening was not as substantial as that seen in diabetes evidence that an inherited microcirculation defect was present before the onset of diabetes led to the hypothesis that such an anatomic change could somehow trigger the development of diabetes [13] Attention shifted away from the relation of capillary changes to diabetic complications and toward their role in causing diabetes Current analyses show that basement membrane measurements are diagnostic neither of diabetes nor pre diabetes Children with ketosis prone diabetes have no basement membrane thickening In adolescent identical twins one of whom had diabetes only the diabetic twin had basement membrane thickening [21] Basement membrane thickens both with advancing age and increasing duration of diabetes [4, 23] Among the Pima Indians individuals who are predisposed to diabetes on a recognizable genetic basis are reported to have basement membrane thickening but their glucose tolerance though normal differs from the Pimas not hereditarily predisposed to diabetes [24]

The two studies supporting a linkage between skeletal muscle basement membrane thickening

nd diabetic retinopathy should be noted with are Kilo and co workers[25] and Yodaiken and ollaborators[26] found both a progression in base nent membrane thickening with duration of iabetes and greater basement membrane thick ning in diabetics with retinopathy In neither tudy was it possible to match individuals with ind without retinopathy for duration of diabetes so that it cannot be firmly concluded that retino pathy rather than duration of diabetes was responsible for the observed increase Skeletal muscle biopsy has little or no use in determining the likelihood of future development of diabetic retinopathy

In addition to the absence of a close relation ship between basement membrane thickening in muscle and evidence of diabetic angiopathy in other body areas no observations yet link thick ening of the basement membrane in the muscle to an impairment of muscle function In skeletal muscle with its low blood flow at rest capillaries remain empty much of the time opening to blood flow mainly on demand Maximal exercise ability is often impaired in diabetics but no one has yet been able to show that basement membrane contributes to the problem even though the base ment membrane is the structure across which all oxygen molecules have to pass to enter muscle It is not illogical to believe that the thickening could impair oxygenation during exercise Changes in diabetic red blood cells also favor disruption of oxygen delivery [2] A careful study showing wheth er diabetic exercise intolerance is more closely related to red cell or basement membrane factors would be very useful to our understanding of both diabetes and exercise

Diabetic retinopathy

The eyes may become severely disrupted in long term diabetes by progressive changes in their vasculature Capillary basement membrane thickening which occurs in parallel with ciliary process basement membrane thickening is not an early or major element in the pathology Hyaline changes in the precapillary arterioles are more important Ashton considers them proba bly to be analogous to capillary basement membrane thickening The development of small areas of non perfused acellular capillaries beyond these hyaline precapillary arterioles is a major event in diabetic retinopathy The affected capil laries normally supply the metabolically active areas deep in the retina The acellular capillary areas regularly become surrounded by microan eurysms Only late in their life do these microan eurysms develop thickening of the basement membrane in their walls

Not yet rigorously proven but important to understanding retinopathy is the proposal that oxygen deprived retinal neurons produce a sub stance which influences blood vessel formation generating microaneurysms venous alterations and even proliferative new vessel growth The substance or substances controlling vascular development would be a major force in causing vitreous hemorrhage and rubeosis iridis as well as producing background retinopathy in response to local hypoxia [29, 3] Evidence in favor of an angio genesis factor is the fact that similar retinal pathology—microaneurysms exudates and pro liferative vascular changes—occurs in other types of retinal ischemia Laser treatment may be effective in retinopathy by restoring the balance between blood supply and metabolic need through reduction of the total amount of retinal tissue

There is evidence that occlusive atherosclerotic changes in one opthalmic artery are associated with increased retinopathy in the eye supplied with less blood [31] In apparent contrast is the report that retinopathy is worse in the eye with the higher intraocular arterial pressure [32] This conflict may be explained if two separate mecha nisms are involved Reduction in blood flow would be expected to aggravate anoxia mediated retinopathy Hypertension may combine with diabetes to increase the rate of development of arteriolosclerosis causing new ischemic areas Either too much pressure or too little flow may well produce the same retinal pathology

Diabetic nephropathy

Rather than being a steady oxygen consumer like the retina the kidney is a filtering system subject to sudden changes in its blood supply While the glomerulus is the structure most strik ingly affected in diabetes the interlobular affer ent and efferent arterioles are altered as well [4] The afferent arteriole is the first structure affected a change said to be a necessary predeces sor to glomerular disease [33] The glomerular base ment membrane is more an epithelial than a vascular structure It is in contact with glomeru lar epithelial cells even in areas away from the capillary lumen Silver staining studies have demonstrated that new basement membrane is

formed principally by the epithelial cells[34] Progressive thickening of the glomerular basement membrane follows the onset of diabetes accompanied by an enlargement of the entire glomerulus[35] The glomerular basement membrane thickening is symmetric, involving the afferent and efferent glomerular areas equally[33] Both glomerular enlargement and basement membrane thickening may be mediated by high growth hormone levels[36] There is no associated diminution in function, glomerular filtration rate is higher than normal in early diabetes, particularly when growth hormone is markedly elevated

Another kind of glomerular change brings about the disruption of glomerular filtration in long standing diabetes An axially placed intercellular substance accumulates in continuity with the hyaline in the *afferent* arteriole The mesangial cells that inhabit the axial area come to be surrounded by islands of amorphous material which appear to be similar to basement membrane but are usually physically separate from it The amorphous axial material is mainly at the afferent end of the glomerulus[37] This extramembranous accumulation is the basis for both diffuse and nodular glomerulosclerosis It causes a progressive distortion of the glomerulus and interacts with basement membrane changes to increase the resistance to blood flow Renal function declines at a point signalled by the development of proteinuria[18]

Diabetics may die from renal insufficiency with kidneys which are larger than normal in size[14] While there is a mild over all loss of glomeruli, many more glomeruli remain at death than are found in terminal glomerulonephritis or pyelonephritis The remaining glomeruli are receiving a sufficient blood supply—the renal cortex is not atrophied Yet almost no filtration is occurring Glomerular deformation and arteriolosclerosis probably combine to lower the glomerular pressure head to below the oncotic pressure of the plasma, blocking filtration and urine formation[38]

Arterial blood pressure affects diabetic nephropathy Kimmelstiel Wilson disease was found only in the kidney receiving full arterial pressure in a hypertensive diabetic who had unilateral occlusive renal arterial disease[39] The kidney exposed to a lower arterial pressure was unaffected A prospective study has shown that when diabetics who develop proteinuria are treated vigorously for associated hypertension there is a slowing of the rate of decline of creatinine clearance[18] If reduced filtration pressure is the most critical issue in the progression of diabetic nephropathy, why should lowering the blood pressure help the situation? Timing may be important When renal insufficiency is well established hypotension reduces urine formation Before renal insufficiency is advanced it is likely that hyaline arteriolar changes induced by hypertension add to the diabetic pathology, further reducing the arterial pressure at the level of the glomerulus

Angiopathy and blood flow

The abnormalities found in diabetic retinopathy and nephropathy demonstrate that not only must blood be pumped from the heart through the arteries to the tissues it must be distributed at an appropriate pressure and oxygen tension to satisfy local metabolic needs Disruptions even at a microscopic level, are sufficient to impair function In diabetes these disruptions are brought about by changes in the walls of blood vessels While the capillary may be easiest to study, it is probably not the area of greatest importance The precapillary arteriole appears to be the structure whose compromise is most disruptive

Local microcirculatory compromise may interact with large vessel disease Circulation to the skin has been studied in diabetes It has been found that maximum blood flow is impaired when diabetic retinopathy is present Diabetics often have severe coronary disease Their intracardiac microcirculatory changes appear to enhance the ischemia produced by atherosclerosis, making cell death more likely once insult has occurred[40] In other chronic disorders microcirculatory changes less pronounced and less destructive than those in diabetes might also interact to contribute to cardiac pathology

Properties of blood altered by diabetes affect the delivery of oxygen Hemoglobin AIc formation and its level in erythrocytes are increased in diabetes[7] Glucose becomes attached to hemoglobin during the erythrocyte's lifetime in the circulation The attachment of glucose to hemoglobin increases its affinity for oxygen so that unless blood flow is increased tissue oxygen tension is lowered Diabetic erythrocytes in addition to hoarding oxygen do not deform as easily

normal erythrocytes when passing through structures smaller than their own diameter[41] Since in many areas of the body the oxygen supplying capillaries are smaller than 8 microns either a larger pressure gradient must be developed or less local flow will occur Both erythrocyte abnormalities contribute to a reduction in the effectiveness of the microcirculation in diabetes even when sclerotic changes are not present Their role in the development of diabetic angiopathy and in enhancing its circulatory disruption is not yet established

A number of studies attempting to reduce the rate of development of complications in diabetes have been carried out Diabetics are subject to both microvascular—neuropathy retinopathy and nephropathy—and atherosclerotic complications—ischemic heart disease and peripheral arterial insufficiency The diabetic of youthful onset has a different morbidity and mortality pattern than the older diabetic He is more subject to microvascular complications and less subject to atherosclerosis In the older diabetic a high proportion of major recognizable sequelae are related to atherosclerotic changes Efforts to modify diabetic complications should take this more fully into account Studies mixing younger and older diabetics may miss the benefit of treatment on the progress of microvascular disease Weight loss is being emphasized in management of the older diabetic While probably beneficial in atherosclerosis weight loss is not known to have any effect on microvascular changes Hypertension in the younger diabetic is quite often a sign of developing diabetic nephropathy while in the older diabetic hypertension may have antedated diabetes and may therefore not aggravate microangiopathy as much The differences in outlook for younger and older diabetics should be taken into better account in selecting subjects in future studies

Improved control of diabetes by multiple doses of insulin reduces progression of diabetic retinopathy Diabetics treated with more insulin have a tendency to gain weight High insulin levels also cause a short term decline in blood volume The stage may now be set for an increased frequency of ischemic heart disease By attacking only diabetic microvascular complications with vigor we may quite conceivably increase the frequency of ischemic vascular disease To avoid such a possibility we are going to have to manage diabetics in such a way that we will prevent atherosclerotic as well as microvascular problems

Summary

Progress in our understanding diabetic angiopathy has been slow but we are now learning a number of lessons of interest to the cardiologist Diabetic angiopathy is a collective term for conditions specific to the diabetic state and related to its duration more than to patient age The angiopathy produces calcification of the media of larger arteries but its major effects are in the microcirculation Intense interest in one feature skeletal muscle capillary basement membrane thickening has dominated the last decade Capillary basement membrane thickening while characteristic of diabetes is associated with little direct impairment of the microcirculation It appears to play no role in the pathogenesis of diabetes itself The pathology of diabetic retinopathy and diabetic nephropathy suggests that arteriolar changes may be the major mediator of diabetic angiopathy This concept is supported by the interactions between hypertension and diabetes in the eye and kidney The course of diabetes of youthful onset differs from that of maturity onset The relative frequency of diabetic angiopathy is higher and of atherosclerotic complications is lower This has made it difficult to demonstrate the potential value of preventive measures Benefit to one type of problem may become hidden by worsening of the other If the diabetic benefits from what is learned about how ischemic heart disease risk can be reduced he will require even more effective management to prevent or control diabetic angiopathy

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Complications due to cloth wear in cloth covered Starr-Edwards aortic and mitral valve prostheses—and their management

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Since the introduction of the ball in cage heart valve prostheses by Harken and colleagues in 1960 and by Starr and Edwards in 1961 the natural history of valvular heart disease has been favorably altered Complications related to prosthetic valve material and design however remain a substantial source of morbidity and mortality[3] The potentially life threatening complications such as ball variance infective endocarditis persistent severe hemolytic anemia systemic arterial embolization thrombotic obstruction of the prosthesis and paraprosthetic regurgitation require prompt detection and aggressive treatment Continued improvement in prosthetic valve material and design has reduced some of these complications For example the problem of ball variance has been virtually eliminated by the use of the hollow metal ball (Stellite 21)[5] The introduction of cloth covered aortic and mitral valve prostheses has substantially reduced the incidence of thromboemboli in patients receiving anticoagulant therapy

Although successful in reducing thromboembolic complications cloth covered valves suffer from a greater degree of hemolysis and problems of cloth wear[5] A varying degree of strut cloth wear is an incidental finding in a majority of patients with cloth covered Starr Edwards aortic valve prosthesis who come for reoperation for infection or periprosthetic leak However clinically significant hemolytic anemia and systemic arterial embolization due to extensive cloth wear have also been described[6,9] The consequences of cloth wear their clinical significance and recognition and their management have not received sufficient attention in the long term management of cloth covered prosthetic valves The following case reports illustrate the clinically significant complications resulting from cloth wear and their correction by replacement of the cloth covered prostheses

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Received for publication May 8 1978

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0002-8703/78/0396-0407$00 80/0 © 1978 The C V Mosby Co

Case reports

Case 1 This 52 year old man was admitted to the New York Veterans Administration Hospital for recurrent strokes Seven years prior to admission he had received a No 11 Model 2300 Starr Edwards cloth covered aortic valve prosthesis for aortic stenosis and insufficiency Six years after valve replacement he suffered sudden onset of left hemiparesis expressive aphasia and left homonymous hemianopsia with nearly full recovery in 2 weeks One year later he suffered sudden onset of right hemiparesis He had no symptoms of diminished cardiac reserve The anticoagulant therapy throughout his postoperative course had been erratic and inadequate Physical examination revealed an afebrile patient with expressive aphasia and mild residual right hemiparesis He was in normal sinus rhythm His blood pressure was 140/90 mm Hg Both carotid pulses were normal and without bruits Prosthetic aortic

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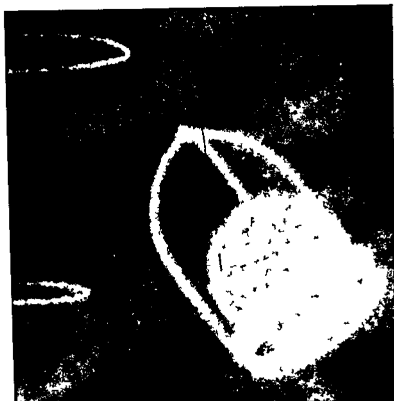


Fig 2 Photograph of a single cine frame from cinefluorographic study of Starr Edwards model 2320 aortic valve in patient No 4 left anterior oblique view Note incomplete seating of the poppet on valve closure with a radiolucent space between the poppet and the adjacent strut and orifice This radiolucent space was present on posteroanterior and right anterior oblique views also

prior to admission for severe mitral stenosis He had been on 10 to 12 5 mg of coumadin daily and his prothrombin time had been one and one half to two times the control during most of his clinic visits Physical examination revealed an afebrile patient He was normotensive and in normal sinus rhythm Both carotid pulses were normal and without bruits The heart size was normal The mitral prosthetic valve closing and opening clicks were normal There was a Grade 2/6 ejection systolic murmur over the aortic area The spleen was not palpable The optic fundi were normal The neurologic examination was within normal limits Blood cultures were negative There was no evidence of mitral prosthetic valve malfunction on fluoroscopy phonocardiography or echocardiography The electroencephalogram and the brain scan were normal Ophthalmodynamometric studies were normal bilaterally Selective right and left common carotid angiograms were normal Cardiac catheterization revealed a resting mean diastolic pressure gradient of 10 mm Hg across the prosthetic mitral valve and mild aortic regurgitation A diagnosis of transient cerebral ischemic attacks (TIAs) due to thromboemboli from the mitral prosthetic valve was made At reoperation the sewing ring of the mitral prosthesis was bare of its cloth covering There was approximately 50 to 60 per cent loss of cloth from the struts Loose threads of cloth were found on the sewing ring No clot was found on the mitral prosthesis or in the left atrial cavity The Starr Edwards mitral valve prosthesis was replaced by a No 29 Hancock porcine xenograft bioprosthesis He has been symptom free postoperatively except for one episode of atrial fibrillation He is not on anticoagulants

Case 4 This 40 year old man was admitted for increasing fatigue weakness and dyspnea on exertion Eighteen months prior to admission he had received a No 10 model 2320 Starr Edwards aortic valve prosthesis for severe aortic valve stenosis His hematocrit was 43 per cent before valve replacement Three weeks after surgery the hematocrit was 28 per cent The reticulocyte count was 27 2 per cent The peripheral blood



Fig 1 Starr Edwards model 2300 aortic valve prosthesis removed from patient No 1 The cloth is completely loose except at the base of one of the struts Note the fragmentation of the cloth along its edges

valve sounds were normal with a Grade 2/6 early systolic murmur There was no diastolic murmur The spleen was not palpable Six blood cultures were negative There was no evidence of aortic prosthetic valve malfunction on fluoroscopy, phonocardiography or echocardiography The perfusion scan of the brain showed defects in both posterior parietal lobes Computerized axial tomography showed evidence of multiple bilateral cerebral infarcts Selective right and left common carotid artery angiograms showed normal cerebral vessels He was reoperated on the presumption that he had had recurrent cerebral thromboemboli from the aortic valve prosthesis At surgery the cloth covering on the struts of the Starr Edwards valve was barely attached at one point on the ring of the prosthesis The rest of the cloth was floating free in the blood stream in the aortic root There was also some loss of cloth fibers from the free edges of the cloth (Fig 1) There was no thrombus on the prosthesis The model 2300 Starr Edwards valve was removed and replaced by a No 23 Carpentier Edwards porcine xenograft bioprosthesis Postoperatively he has required permanent pacemaker implantation due to syncope from sinus arrest Sixteen months after reoperation he has not had any episode of systemic emboli

Case 2 This 61 year old man received a No 11 model 2320 Starr Edwards aortic valve prosthesis on Oct 25, 1973 for severe aortic regurgitation Eighteen months after valve replacement while not anticoagulated, he suffered right upper extremity paresis from which he fully recovered He was adequately anticoagulated with coumadin after this episode Four years and 2 months after valve replacement he began to have episodes of "feeling ill at ease, 'glare in the left eye, and transient loss of memory This was followed by sudden onset of weakness of the right hand that lasted for 15 minutes His prothrombin time was 27 3 seconds to a control of 12 4 seconds when he suffered this episode Physical examination revealed an afebrile patient He was in chronic atrial fibrillation Both carotid pulses were normal and without bruits The neurologic examination was within normal limits Cardiac auscultation revealed a high pitched metallic quality of the prosthetic valve opening and closing clicks When asked the patient admitted to having noticed a change in quality and loudness of the valve sounds A Grade 2/6 ejection systolic murmur was present There was no diastolic murmur The spleen was not palpable Blood cultures were negative The electroencephalogram and the brain scan were normal There was no evidence of prosthetic aortic valve malfunction on fluoroscopy phonocardiography or echocardiography He was reoperated because of recurrent cerebral thromboemboli presumably arising from the aortic valve prosthesis At surgery the aortic valve prosthesis showed extensive cloth wear along the struts with exposure of the metal A small 3 mm deposit of a white thrombus was present on one of the struts The left atrium was examined and no clot was found in the left atrial cavity The Starr Edwards aortic valve prosthesis was replaced by a porcine xenograft bioprosthesis Postoperative recovery was poor in this patient due to pulmonary infection in the early postoperative period and serum hepatitis 4 months after surgery He was taken off anticoagulants 2 months after surgery He has not had any episode suggestive of systemic embolization since reoperation

Case 3 This 40 year old man was admitted to the New York Veterans Administration Hospital for two episodes of transient blindness in the left eye in one month He had received a model 6320 Starr Edwards mitral valve prosthesis 7 years

thus leaving an intravalvular open space through which mild aortic regurgitation was noted Thus the radiolucent space seen on fluoroscopy between the poppet and the valve ring and the adjacent strut probably represented loss of cloth in this area leading to incomplete seating of the poppet There was no thrombus on the valve The Starr Edwards aortic valve prosthesis was replaced by a porcine aortic xenograft bioprosthesis. His hematocrit has increased to 41 per cent postoperatively and he is asymptomatic He is not on anticoagulants

Case 5 This 21 year old man had received a No 10 model 2320 Starr Edwards aortic valve prosthesis for severe aortic regurgitation His preoperative hematocrit was 47 per cent One month after valve replacement his hematocrit had decreased to 36 per cent and the serum LDH level was 740 units per ml He was on coumadin and his prothrombin time was 29 5 seconds to a control of 11 6 seconds Ten months after valve replacement he was admitted for severe fatigue and exertional dyspnea Physical examination revealed an afebrile patient The prosthetic aortic valve opening and closing clicks were normal There was a Grade 3/6 harsh ejection systolic murmur all over the precordium A Grade 2/6 high pitched decrescendo early diastolic murmur was also heard along the left sternal border The spleen was not palpable The hematocrit was 16 5 per cent and the serum LDH was 2 400 units per ml The peripheral blood smear showed many fragmented red blood cells and poikilocytes The serum iron and iron binding capacity were 64 mg per cent and 414 mg per cent Stool examination was negative for occult blood Urine hemosiderin was 4+ Direct and indirect Coomb s tests were negative Severe hemolytic anemia due to traumatization of red cells over the aortic valve prosthesis was diagnosed Phonocardiogram revealed normal prosthetic aortic valve opening and closing clicks along with the systolic and diastolic murmurs described on auscultation The echocardiogram revealed a slightly enlarged left ventricle with normal ejection fraction and fine diastolic fluttering of the anterior mitral leaflet consistent with aortic regurgitation Fluoroscopy revealed incomplete seating of the poppet on the ring during valve closure and marked transverse rocking motion of the poppet during valve opening His hematocrit increased to 36 per cent after multiple blood transfusions and he was reoperated 11 months after valve replacement At surgery the Starr Edwards aortic valve prosthesis showed extensive cloth wear on all struts and one of the struts was completely denuded of its cloth covering There were several small cloth fibers attached loosely to the valve ring There was no thrombus The Starr Edwards prosthesis was replaced with a No 21 Hancock porcine xenograft bioprosthesis He has been asymptomatic 12 months after reoperation His hematocrit is 50 per cent He is free of cardiovascular symptoms and does not take anticoagulants

Discussion

Incidence of cloth wear Braunwald and Bonchek [9] first demonstrated that covering of rigid prosthetic heart valves with porous cloth encourages autogenous tissue growth to cover the valve prosthesis Such coverage by autologous tissue prevents the blood and tissue–metal interface and makes thrombus formation unlikely Long term postoperative follow up of patients with cloth covered Starr Edwards aortic and mitral valve prostheses has shown significant reduction in the incidence of thromboembolism in the presence of anticoagulant therapy when compared with patients with non cloth covered valves [3] However wear of cloth in the areas struck by the metal poppet has been an inherent problem The true incidence of cloth wear in general and that of clinically significant cloth wear is not definitely known Starr and coworkers[3] reported that 12 out of 18 patients with cloth covered aortic valves (models 2310 2320) who were reoperated for perivalvular leak hemolytic anemia infection or thrombotic obstruction of the prosthesis showed evidence of strut or orifice cloth wear More importantly four of these 12 patients were reoperated for hemolytic anemia and all four patients had strut cloth wear Isom and associates have reported that the incidence of clinically significant cloth wear is probably less than one per cent in their experience At the New York Veterans Administration Hospital four of 121 (3 3 per cent) survivors with cloth covered Starr Edwards aortic valve prostheses and one of 83 (1 2 per cent) survivors with cloth covered Starr Edwards mitral valve prostheses have been reoperated for consequences of cloth wear an over all incidence of 2.5 per cent Although the incidence of clinically significant cloth wear is small its early recognition and

Table I Clinical and operative findings

Case No	Model and size of Starr Edwards valve prosthesis	Duration since valve replacement	Chief complaint	Operative finding
Systemic emboli				
1	2300 No 11	7 years	2 CVAs	Cloth covering barely attached to the orifice at one point rest of the cloth floating in blood stream loss of fibers at edges of the cloth
2	2320 No 10	4 years and 4 months	Transient loss of memory monoparesis	Extensive cloth wear on all struts small 3 mm white thrombus on one strut
3	6320	7 years and 8 months	Amaurosis fugax	50% to 60% loss of cloth from the struts cloth covering the orifice almost completely shredded
Hemolytic anemia				
4	2320 No 10	6 months	Fatigue exertional dyspena	Extensive cloth wear on all struts one strut completely bare of its cloth covering
5	2320 No 10	18 months	Fatigue dark urine after exercise	Extensive cloth wear on the inner surface of all struts

CVA = cerebrovascular accident

Table II Findings that should arouse suspicion of cloth wear

1 Recurrent transient cerebral ischemic attacks or other systemic emboli despite adequate anticoagulation
2 Systemic arterial embolization more than 4 years after valve replacement with cloth covered prosthesis
3 Increase in loudness of the prosthetic valve clicks on auscultation particularly with a metallic pitch
4 Persistent severe hemolytic anemia with or without regurgitation across the prosthesis
5 Incomplete seating of the poppet on the valve orifice seen on cinefluorography or intravalvular regurgitation seen on angiography

smear showed many fragmented red blood cells Serum SGOT was 117 units per ml Serum LDH was 2,550 units per ml Free serum hemoglobin was 122 mg per cent There was 4+ hemosiderinuria Stool examination was negative for occult blood Direct and indirect Coomb s tests were negative Diagnosis of hemolytic anemia due to excessive trauma to the red cells was made He was placed on Ferrous sulfate 325 mg three times a day and advised to refrain from vigorous physical activities Folic acid 2 mg daily was added to the therapy later on Nine months after valve replacement his hematocrit was 27 per cent Bone marrow examination revealed no stainable iron stores Eighteen months after valve replacement, he was admitted to the New York Veterans Administration Hospital for reoperation because of persistent hemolytic anemia despite restricted physical activity iron and folic acid therapy Physical examination revealed an afebrile patient He was normotensive and in normal sinus rhythm. Prosthetic aortic valve sounds were normal A Grade 2/6 ejection systolic murmur was heard all over the precordium There was no diastolic murmur The spleen was not palpable Blood cultures were negative Prothrombin time was 23 8 seconds to a control of 12 6 seconds There was no evidence of prosthetic aortic valve malfunction on phonocardiography and echocardiography The left ventricular ejection time index was normal Cardiac fluoroscopy revealed a well anchored prosthesis ring and a smooth poppet The poppet motion showed marked lateral oscillations during opening and closing movement The seating of the poppet at the time of valve closure revealed a persistent radiolucent space between the poppet and the valve ring and between the poppet and the adjacent strut (Fig 2) A gated cardiac blood pool scan showed the left ventricle to be of normal size with an ejection fraction of 84 per cent At surgery the Starr Edwards aortic valve prosthesis showed severe cloth wear along the inner surface of all the struts The seating of the poppet on the ring at the time of valve closure showed loss of cloth on the strut and the corresponding area of the ring

ics such as obstruction or regurgitation across the prosthesis but these technics do not detect presence of clot or cloth wear on the prosthesis However incomplete seating of the poppet caused by cloth wear may permit intravalvular regurgitation The demonstration of intravalvular regurgitation by angiography in patients with cloth covered metal ball valvular prostheses should arouse suspicion of cloth wear

The clinical findings which should arouse suspicion of clinically significant cloth wear are summarized in Table II The incidence of thromboembolism is highest in the first two years after valve replacement decreases during third and fourth year and is uncommon after four years Thus recurrent systemic arterial embolization despite adequate anticoagulation more than four years after valve replacement may favor cloth fiber emboli rather than thromboemboli as was the case in our patients (No 1 2 and 3)

Management of suspected cloth wear Asymptomatic patients with suspected cloth wear should be observed carefully for development of serious complications When medically untreatable complications develop aggressive treatment with reoperation becomes necessary Recurrent systemic emboli despite adequate anticoagulation and severe hemolytic anemia are the clinically significant consequences of cloth wear that can be corrected by reoperation At reoperation the valve may be replaced by the newer model composite strut Starr Edwards valve (2400 aortic and 6400 mitral) or by porcine xenograft bioprosthesis The composite strut Starr Edwards valves are reported to be noisy and require long term anticoagulation[3] However they produce a lesser degree of hemolysis and strut cloth wear does not occur[3] At the New York Veterans Administration Hospital all five patients reoperated for cloth wear have received porcine xenograft bioprostheses Actuarially determined over all survival rates of patients receiving xenograft valves in both the aortic and mitral positions are comparable to the survival rates reported by Bonchek and Starr[3] with cloth covered composite seat prostheses[7] The incidence of thromboembolic events is less with xenograft valves and the majority of thromboemboli have occurred in the early 6 to 12 week postoperative period Thus anticoagulant therapy is recommended during the 6 to 12 weeks after insertion of xenograft valves in the aortic or mitral position after which period anticoagulation is not necessary except in the presence of large left atrium and chronic atrial fibrillation

Summary

Five cases of complications due to cloth wear in cloth covered composite seat Starr Edwards aortic and mitral valvular prostheses are described The complications of cloth wear were recurrent systemic emboli in three patients two with aortic and one with mitral prosthesis and severe hemolytic anemia in two patients with aortic prosthesis The over all incidence of clinically significant complications due to cloth wear in aortic and mitral valve prosthesis was 2 5 per cent The diagnosis of cloth wear is impossible before reoperation and it was made by exclusion of other causes of recurrent transient cerebral ischemic attacks or systemic emboli and by exclusion of other causes of hemolytic anemia Clinical and laboratory findings suggestive of cloth wear are described Aggressive management of complications of cloth wear by reoperation is likely to prevent disabling or lethal consequences Porcine xenograft aortic and mitral bioprostheses were used in these patients to replace the cloth covered valvular prostheses The symptoms due to cloth wear were abolished in all patients by reoperation and all patients are off anticoagulants post operatively The operative mortality rate for reoperation in this small group of patients was zero

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aggressive treatment can prevent disabling or lethal consequences

Consequences of cloth wear The two major complications due to cloth wear are cloth fiber emboli to the systemic circulation and hemolytic anemia with or without regurgitation across the prosthesis, as illustrated by the above described case reports The clinical and operative findings in these patients are summarized in Table I Starr[1] has stated that three out of four patients who are reoperated following aortic valve replacement with cloth covered aortic valves show evidence of cloth wear, perhaps asymptomatic The consequences of cloth wear may vary from minor events such as transient cerebral ischemic attacks without residua to serious ones such as recurrent cerebral embolism[7,8] paravalvular leak,[6] severe hemolytic anemia,[7] and even sudden death[13] Although absolute confirmation of cloth fiber systemic embolism is impossible in the absence of examination of the involved organs, postmortem studies have demonstrated Teflon emboli in multiple peripheral organs[9] Cloth fiber emboli can occur with either aortic or mitral valve prosthesis while clinically significant hemolysis is associated only with the aortic prosthesis Clinically significant hemolysis has not been a problem with the mitral prosthesis[14]

Diagnosis of cloth wear The diangosis of clinically significant cloth wear should be suspected in any patient with cloth covered valvular prosthesis who has recurrent systemic emboli despite adequate anticoagulation or who has hemolytic anemia with or without regurgitation across the prosthesis The absolute confirmation of cloth wear being responsible for emboli or hemolytic anemia can only be made at reoperation Hence, all other causes of systemic emboli or hemolytic anemia should be first excluded Since a vast majority of systemic emboli present as recurrent transient cerebral ischemic attacks it is important to exclude extracranial carotid artery disease as well as intracranial space occupying lesions which may produce similar symptoms This may be accomplished by electroencephalography perfusion scan of the brain computerized axial tomography and common carotid arteriography as in patients No 1, 2 and 3 Carotid angiography may not be necessary if ophthalmodynametry is normal bilaterally Infective endocarditis of the prosthesis is another important cause of systemic emboli that should be ruled out Absence of fever and splenomegaly, absence of new murmur, and negative blood cultures usually exclude infection of the prosthesis In patients with anemia, complete hematologic work up is necessary to confirm that it is caused by red cell traumatization around the prosthesis Presence of schistocytes on peripheral blood smear and elevated serum LDH level with negative Coombs test usually confirm that the hemolytic anemia is related to the valvular prosthesis

Cinefluorography of the prosthetic valve showed marked lateral oscillations of the poppet on valve opening and incomplete seating of the poppet on valve closure in both patients with hemolytic anemia (Cases No 4 and 5) These may be important clues suggesting cloth wear As the cloth on the inner surface of the struts is worn out, the internal diameter of the cage would increase, permitting excessive play on the poppet leading to lateral oscillations as it moves from the seat to the apex of the cage on valve opening Loss of cloth from the strut and the adjacent orifice may be responsible for the incomplete seating of the poppet, thus producing a radiolucent space between the poppet and the strut as shown in Fig 2

Phonocardiography is helpful in detecting changes in amplitude and timing of prosthetic valve opening and closing clicks and in detecting new murmurs[15,16] Since cloth wear most commonly occurs along the inner aspect of the struts, development of louder valve clicks particularly with a metallic pitch on auscultation (as metal poppet strikes against metal struts) as observed in case No 2, should arouse suspicion of cloth wear

Echocardiography alone or combined phonoechocardiography of the valvular prosthesis further assists in the evaluation of its mechanical function This technic is particularly valuable in evaluation of the mitral valve prosthesis[17] Evaluation of the aortic valve prosthesis is much more limited due to technical difficulties in recording satisfactory echocardiograms[18] Echocardiograms of the valvular prostheses in all five of our patients were unremarkable Thus there are no specific echocardiographic features that suggest presence of cloth wear

Cardiac catheterization and angiocardiography provide information regarding the hemodynam

Annotations

Spontaneous changes in the severity of angina pectoris*

Angina is known to be affected by many extra cardiac factors such as changes in the weather changes in body weight the development of anaemia cervical spondylosis duodenal ulcer ation and disease of the biliary tract But sometimes angina becomes steadily worse in the absence of any recognizable extra-cardiac factor and sometimes it gradually subsides and disappears. How common are these spontaneous changes in the severity of angina and what is their outcome?

Three hundred and seventeen patients with angina associated with ischemic heart disease were followed until death or until an average of six and a half years had elapsed from the onset of their symptoms (Cases in which the angina was due to valvular heart disease or non coronary cardiomyopathy were excluded.) The male/female ratio was 1 3 1 and the median age for the onset of angina was in the sixth decade for men and in the seventh decade for women

Crescendo angina In 84 patients (a little over a quarter of the total) the angina became progressively more easily induced in the absence of any detectable extra cardiac factor and without change in treatment In half these patients (41) the crescendo phase culminated in myocardial infarction or sudden death in the remainder it gradually subsided to its previous level of intensity In a few instances the crescendo phase was associated with evidence of heart failure or deterioration in the electrocardiogram suggesting a small myocardial infarct or coronary thrombosis but in the majority there was no objective clinical evidence of deterioration in the cardiovascular system

The crescendo phase was found to develop at any time from the first week to as long as 33 years after the onset of the angina The interval between the onset of the crescendo phase and the development of incapacity ranged from two days to almost a year in half the incapacity developed within a month, and in three-quarters within three months

It is difficult to compare our findings with those of previous workers, because cases of crescendo effort angina have usually been included with cases of recent onset effort angina and cases of spontaneous angina at rest in a group now commonly referred to as unstable angina The valuable reports of Levy and Duncan and associates illustrate this problem Levy reviewed the course of 158 patients with what he called changing patterns of angina" and found that nearly 40 per cent proceeded to myocardial infarction or sudden death. Duncan and colleagues studied the natural history of 251 patients with what they termed new or worsening angina and found that only 16 per cent developed myocardial infarction or died suddenly An important difference between the two series lies in the relative proportion of cases of recent onset angina and crescendo angina Cases of crescendo angina formed 67 per cent of Levy s series whereas they accounted for only 41 per cent of the Edinburgh series Both reports are consistent with our finding that approximately half the patients developing spontaneous crescendo angina proceed to myocardial infarction or sudden death.

Spontaneous subsidence of angina In 55 patients (one sixth of the total) angina ceased spontaneously for at least some months (without the development of myocardial infarction) and in half (28) of these it had not returned by the end of the period of observation In two thirds of the cases the subsidence occurred within a year of the onset but three patients lost their angina after it had been present for three years and one after ten years Those whose angina subsided did not differ from other patients with angina in respect of sex or associated hypertensive heart disease Rather more than average had a normal previous electrocardiogram yet almost half had evidence of previous myocardial infarction or a major electrocardiographic abnormality

In the Framingham Study angina was noted as ceasing spontaneously in 30 per cent of subjects This is almost double the proportion in our series but the Framingham Study probably included patients with angina which was too mild to necessitate referral for cardiological advice In any case it is clear that a considerable proportion of patients with angina do lose their symptoms even after the angina has been present for several years. It is possible that this natural tendency is counteracted by recalling patients for frequent follow up examination with the consequent focusing of their attention on their hearts.

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*We are indebted to the British Heart Foundation for a generous grant in support of this study

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Spontaneous changes in the severity of angina pectoris*

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Of discoveries

The great advancements in science and knowledge are not planned and are rarely if ever the product of previously outlined plans of large research programs The great discoveries are unexpected and no one can control them or has had a monopoly on them To realize this one merely has to reflect upon the great scientific discoveries and advancements in science and knowledge of the past e g polarized light by Nicol x ray by Roentgen natural radiation by Henri Becquerel and Curie and the vacuum tube by DeForest to list a few

An article in *Science* of August 1 1975[1] describes an interesting situation that led to an important and unplanned discovery in astronomy which culminated in the Nobel Prize Award for Physics To quote the article in *Science* perhaps the most dramatic scientific event of the decade was the discovery in 1967 of the celestial objects known as pulsating radio stars or pulsars [1] These objects were determined to be neutron stars embers of stellar activity and barely detectable on earth This was a serendipitous discovery by Jocelyn Bell (now Mrs Burnell) a 19 year old graduate student training under Anthony Hewish at the University of Cambridge in England The 1974 Nobel Prize in Physics was awarded to Anthony Hewish supervisor of Jocelyn Bell for the discovery of pulsars and to Martin Ryle founder of the Cavendish Laboratory radioastronomy team at Cambridge for his research in radio astrophysics

The events and details of research in the laboratory leading to the discovery of pulsars are interesting They summarize the influence of scientific bureaucracy in the world today The events that led to this most important discovery are presented in the *Science* article and in the lecture delivered by Anthony Hewish when he received the Nobel Award Apparently the first observation of a pulsar occurred in August 1967 and the discovery was first reported during February 1968 The five authors of that report included Hewish and Bell and four others were acknowledged for their assistance with the report including Sir Martin Ryle However of extreme interest is the fact that this important discovery was made by Miss Bell an unknown inexperienced graduate student and research trainee

Miss Bell first noted and recognized the significance of the signals which emmanated from certain stars After Professor Hewish became convinced of the genuine nature and importance of her observations he supervised the follow through of the discovery Despite some controversy concerning the Nobel Prize Award Mrs Jocelyn Bell Burnell remains satisfied that the award was given to Professor Hewish who had to take all the risks and who readily acknowledges that the pulsars were first found by Mrs Burnell

The manner in which this award winning discovery was made by a novitiate in research presents an interesting tale which is briefly summarized here As a graduate student Miss Bell helped construct the 4½ acre radiotelescope used in her discovery She operated the new telescope and had to study and analyze for her Ph D thesis strip chart data which poured out at a rate of 96 feet per day or 400 feet of triple tract trace per one complete coverage of the sky After beginning the recordings in July, 1967 Miss Bell had a backlog of 1 000 feet of chart to be analyzed by October and by December she had a backlog of ⅓ mile She scanned the tracings by eye and happened to note a bit of scruff ¼ inch long on a lengthy 400 foot chart which she could not classify as artifacts from man made sources This observation was different and new to her and she tried diligently to follow up on the scruff Professor Hewish was first of the opinion that the pulsations represented a flare star that had been missed He insisted on several occasions that it was an artifact and unimportant. But Miss Bell reported further recording of the scruff to Professor Hewish consisting of a series of pulses 1 ⅓ seconds apart Because of this extremely fast rate it was difficult to believe that the source was not man made Hewish later confirmed, after review of the recordings following the perseverance of Miss Bell that the pulses followed sidereal time By contacting other observatories Hewish ruled out the possibility that the scruff was due to other astronomical equipment generating electrical interference at a fixed sidereal time Even the idea of a civilization from another planet signalling the earth was considered and was ruled out when the only Doppler shift noted was that due to motion of the earth alone In her logbook Miss Bell referred to the source as Belisha beacon the nickname for pedestrian traffic signals in London

A second and different source of pulsations with a period of 1 ¼ seconds was discovered by Miss Bell in December 1967 Hewish confirmed this second source in January and it became obvious to Miss Bell and Professor Hewish that the pulses represented recordings from very rapidly rotating stars. Before their paper describing the discovery was submitted for publication in February they had recorded two more similar sources These observations remained a closely guarded secret until announced by Hewish at a seminar at Cambridge and published in *Nature* Miss Bell was forced to discontinue these studies to write her Ph D thesis and the discovery appeared only as an appendix in her thesis

In retrospect Mrs Burnell (nee Jocelyn Bell) notes that the most difficult aspect of this momentous discovery of x radiation in astronomy was the detection of the scruff on the 400 feet of triple trace chart paper and except for her perserverence the pulses would have been dismissed as man made artifacts

Should Mrs Burnell have shared the Nobel Prize awarded Hewish and Ryle? The Franklin Institute of Philadelphia awarded its Albert A Michelson medal to Hewish and Burnell jointly in 1973 Mrs Burnell obviously understood what she was doing in her research and she was not told in advance to look for "pulsars nor was this a part of the experimental protocol This was a discovery not even sought after

So what about awards honors and appointments to select groups or societies in science? And what about scientific bureaucracy?

The opinion of astrophysicists throughout the world concerning Jocelyn Bell Burnell s discovery of September 1967 was clearly made evident at the Texas Conference held in Boston in December 1976 The organizing group of the Texas Symposium on Relativistic Astrophysics invited her to be the featured after dinner speaker at their banquet Tom Gold of Cornell University introduced her as having made "perhaps the greatest single discovery in astronomy in this century After her speech she was extended a standing

ovation for her discovery by the 400 astrophysicists in the audience She had not visited the U S previously and would have not been able to attend the symposium except for the invitation extended to her She was not envious of the Nobel decision and even expressed her opinion that the supervisor should receive both credit and blame for a graduate student s results Besides she said at the banquet it s no skin off my nose look at the company I m in [5]

Such is the reward of research and of awards

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The carbon copy pain of myocardial infarction*

It is a matter of considerable practical importance to decide whether an episode of spontaneous chest pain in a patient with a history of angina is cardiac or not Patients with angina tend to be abnormally aware of sensations in the chest which others would ignore so that this is a problem which not uncommonly presents itself to doctors

Most authorities state or imply that the site of the pain in myocardial infarction is identical with that of angina though it has long been recognized that the pain of infarction may be felt in the epigastrium

Three hundred and thirty patients with angina pectoris were followed until death or until an average of six and a half years had elapsed from the onset of their symptoms The site of the anginal pain though differing from patient to patient was constant for each individual except that it tended to spread to other parts of the torso if the attacks were severe Among the 330 patients studied there were 145 in whom the site of the anginal pain had been precisely recorded and who subsequently developed myocardial infarction In 136 (94 per cent) the epicenter of the pain of infarction was similar to that of the preceding angina (though the pain often extended more widely) This was true even when the site of angina had been unusual e g in the right side of the chest or the back In nine (6 per cent) of the patients however the pain of infarction had a different epicenter from that of the preceding angina In each of these nine ca es the pain of infarction was lower than (caudal to) that of the angina Thus if the pain of angina had been felt in the upper chest that of infarction was felt in the mid chest if the pain of angina had been felt at the lower end of the sternum that of infarction was felt in the epigastrium Many of our patients developed pains which were lateral to or at a hi her site than that of their angina but in such cases there was never any evidence of acute cardia ischemia or infarction however severe the pain might be

Thus the pain of infarction may be thought of as a carbon copy of the angina the copy being usually more intense than the original and occasionally slipping to a lower level Pain which does not have the same epicenter as the angina or is not immediately below it is unlikely to be cardiac in origin

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*We re ind bted to the British Heart Fo nd t n f a g ero grant in support f this study

The effect of a new beta blocking agent levo-bunolol on exercise induced or augmented ventricular arrhythmias*

The control of ventricular ectopic arrhythmias continues to be a significant clinical pr blem Recent studies have stressed the inefficacy of conventional drugs and the high incidence of their deleterious sid effects In addition these reports have stressed the need to demonstrate efficacy through exercise stress and/or long term monitoring rather than with brief routine electrocardiograms

*This work was supported in part by a grant fr m th V terans Administration.

We carried out an open pilot placebo controlled study to determine the effect of a 2 mg single oral dose of a new beta adreno blocking agent levo bunolol* on exercise stress induced or augmented ventricular ectopic activity (EIAVEA) Levo bunolol is 40 times as potent as propranolol by weight and appears to have a longer duration of action on exercise capacity in angina pectoris Patients studied were seven male volunteers aged 43 to 60 years known to develop ventricular ectopic activity during or within 6 minutes after exercise The developed arrhythmias were either premature ventricular contractions greater than 10 per minute couplets runs (three or more sequentially) bigeminy or multifocal beats On each of two study days at least 3 days apart each patient took the prescribed medication placebo or drug and was exercised exactly 2 and 4 hours after dosing The criteria for effectiveness was reduction (> 50 per cent) or elimination of the EIAVEA by the active drug There were no adverse effects observed Five of seven patients had gross improvement in their EIAVEA One patient had insignificant suppression of EIAVEA Another patient who after placebo had frequent premature ventricular contractions at rest with little augmentation by exercise had < 50 per cent suppression at rest and during exercise

These results were comparable to similar studies carried out with propranolol[5] It appears advantageous to utilize this class of drugs initially in suitable patients instead of quinidine and procainamide which under similar circumstances have been less effective and were associated with frequent side effects The potential advantage of levo bunolol consists of its greater potency both by weight and in duration of action

The relationship between high grade ventricular ectopic activity and sudden cardiac death remains to be absolutely proved Circumstantial data pointing to such a causal relationship has been reasonably impressive In addition many of these patients report disturbing symptoms with activity which would justify suppressive therapy In our experience propranolol and probably levo bunolol are effective agents for the suppression of EIAVEA in selected patients and were not complicated by serious adverse effects thus far

*Kindly supplied by Warner Lambert Inc

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Letters to the Editor

Truncus arteriosus in a family

To the Editor

We wish to report a family in which three out of four siblings were born with persistent truncus arteriosus This lesion is a very rare cardiovascular anomaly representing only 04 to ?0 per cent of all congenital heart defects A brief discussion of possible etiologic factors is presented

Case 1

The first patient (IV 1 Fig 1) was a full term 4170 Gm male born to a 17 year old P O O O O mother The pregnancy was complicated by excessive maternal weight gain and pedal edema She was treated daily with an unspecified diuretic from the fifth month until term

The neonatal period was marked by poor feeding dyspnea sweating and cyanosis with crying Cardiac catheterization data were compatible with truncus arteriosus Type II Medical management with digitalis and diuretics was unsuccessful and pulmonary artery banding was performed at nine weeks of age Despite the banding the infant continued to deteriorate and died on the second postoperative day At autopsy a Type II truncus arteriosus was found No other anomalies were present.

Case 2

The second patient (IV 2, Fig 1) was a female born following a normal 37 week pregnancy The mother was now 18 years old Birth weight was 2475 Gms On the first day of life mild cyanosis was appreciated but vital signs were normal. Over the following days mild congestive heart failure developed and the infant was treated with digitalis and Lasix Cardiac catheterization and angiography were performed on the sixth day of life The findings were compatible with truncus arteriosus Type II The baby was managed medically but congestive heart failure persited She was scheduled for surgery but sustained a cardiac arrest and died on the 23rd day of life Autopsy examination revealed truncus arteriosus Type II Non-cardiac anomalies included a hydronephrotic left kidney with double ureters an absent gall bladder fibrosis and hemosiderosis of the liver

Case 3

Patient 3 (IV 4 Fig 1) was a female born after an uncomplicated 42 week pregnancy Birth weight was 3360 Gms The mother was now 21 years old and gravida 4 At age 20 she had given birth to a 3 900 Gm male who is normal

The baby became cyanotic at six hours of age and a holosystolic murmur was heard She subsequently developed evidence of congestive heart failure Cardiac catheterization and angiography were compatible with a truncus arteriosus Type III The infant did not respond to vigorous anticongestive therapy and underwent left pulmonary artery banding on the 13th day of life Several hours later she had a cardiorespiratory arrest and could not be resuscitated Autopsy findings revealed a truncus arteriosus Type III

The family history (Fig 1) was significant in that the father (III 7 Fig 1) had a patent ductus arteriosus which was ligated at 5 years of age He also has diabetes mellitus treated with insulin A maternal uncle (II 5 Fig 1) died at the age of 9 months due to an unspecified congenital heart defect An autopsy was not performed

Discussion

The etiology of most congenital heart defects is believed to be multifactorial i e genetic predisposition plus an environmental insult during a critical period of cardiac development Some cases, for example idiopathic hypertrophic subaortic

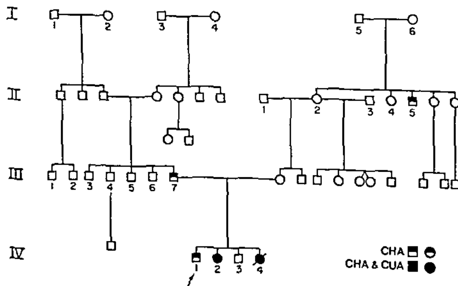


Fig 1 Diagram representing family tree *CHA* = congenital heart anomaly *CUA* = congenital urinary tract anomaly *Oblique line* (IV-4) = genital anomaly

stenosis[2] and Marfan s syndrome[3] are transmitted as autosomal dominants Familial occurrence of congential cardiovascular defects suggestive of a polygenic inheritance include hypoplastic left ventricle[4] tetralogy of Fallot and atrial septal defect[5] In some children the nature of the cardiovascular anomaly is predictable as part of a chromosomal abnormality or a constellation of defects representing a specific syndrome[7] and in others environmental factors are implicated the most documented being thalidomide[8] and rubella virus

The etiology or mode of transmission of truncus arteriosus is not known The presence of the same defect in three of four siblings whose parents do not have the defect suggests a recessive mode of inheritance It is of interest that both parents have a grandmother born in Ireland but no further evidence to support consanguinity is present

The father had a patent ductus arteriosus which is a very common anomaly and is unlikely to be related to the occurrence of truncus arteriosus in his offspring The mother did not take any medications during the first trimester of any pregnancy The father is a warehouse worker and no contact of either parent with any chemicals or other teratogenic agents could be established A seasonal association[10] is unlikely since two of the affected infants were born in April a healthy sibling in March and another infant with truncus arteriosus was born in August

Maternal diabetes mellitus has been associated with congenital anomalies of the great vessels in offspring but no such relationship in infants born to diabetic fathers has been shown In this family the data strongly suggest that a recessive inheritance though a multifactorial cause cannot be completely excluded

Addendum

Since this letter was submitted a fifth infant was delivered who died on the second day of life following repair of a diaphragmatic hernia At autopsy left pulmonary hypoplasia and a small ventricular septal defect were found Chromosome studies of this infant and of Case 3 were normal

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Serum myoglobin tests by RIA

To the Editor

The article in your highly esteemed AMERICAN HEART JOURNAL on Serum myoglobin determinations by radioimmunoassay from the group in Dallas (Vol 95 page 0 January 1978) deserves comment from a practicing Pathologist

Throughout the paper the statements are made within four hours the four hour radioimmunoassay a four hour test the four hour shortened method These numbers are just not true

The numbers do not account for the numerous steps prior to the incubation (THE FOUR HOUR INCUBATION) such as the Emergency Room doctor requesting of the Emergency Room clerk the notification of the Laboratory the Laboratory person getting to the Emergency Room identifying the patient and obtaining the blood the clotting of the blood which can vary remarkably if the patient is on anticoagulants the obtaining of the serum and the preparation of the RIA tubes Subsequent to the FOUR HOUR INCUBATION there is precipitation with centrifugation and radiation counting (which may vary according to the intensity of the I label) All theses steps are based on the immediate availability of people veins equipment (centrifuges especially) and telephones

The true time from notification to the Laboratory to reporting the results of the test to the doctor will range from over 5 to over 6 hours

The expenses of performing this RIA test on the serum of one patient at a time are also very high

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Nocturnal angina

To the Editor

Despite its potential interest the article on nocturnal angina by Lichstein and associates (AM HEART J 93 723 1977) contributes little to our understanding of the topic First the method used namely retrospective query of past angina conducted at time of admission for acute myocardial infarction is grossly subjective and of questionable scientific value The authors fail to furnish a patient age range in their data When dealing with subjects over the average age of 58 years one questions the reliability of recall vs age especially when reviewing 174 unselected and consecutive cases Thus one also is reluctant to accept interpretation based on a potentially unreliable group of 23 study patients in a field of 174 Again the authors furnish no information regarding treatment of selected patients during nocturnal anginal episodes Perhaps inadequate or even excessive therapy was responsible for the angina irrespective of the type of the ultimate infarct Finally in the discussion the comparisons of infarct types have no relation to the topic and the authors explanations for nocturnal angina apply as well to any type of angina

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REFERENCE

1 Lichstein E Alosilla C Chadda K D and Gupta P K Significance and treatment of nocturnal angina preceding myocardial infarction AM HEART J 93 723 1977

Quality of early ECG tracings

To the Editor

In the early twenties the electrocardiogram became a valuable aid to cardiologists all over the world In that period I worked in the Leiden University Hospital with an original Einthoven string galvanometer What strikes me now is the poor quality of many of the electrocardiograms made with modern machines Only few are comparable in quality with those obtained by Einthoven Improvement of the frequency characteristics of the whole system mainly due to less inertia in the recorder (possibly direct recording from a cathode ray tube on film) might bring us back to the good standard A challenge to industry to the benefit of cardiac patients!

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†Dr Kleyn passed away on March 26 1978 while this letter was at the printers.

Hypertension control an alternate view from Gimbels

To The Editor

We share the concern of Professor Sackett and associates about the risks that confront those students of hypertension who emerge from the laboratory or ward and venture out into the community Since the Gimbels program was specifically mentioned its sponsors were presumably among those feared to be abandoning scientific method for (a) collection of hopes homilies, and unconfirmed conventional wisdom" While pleading guilty to harboring in our innermost thoughts a glimmer of hope we are unwilling to concede that our papers contain a single homily nor did we ever lay claim to wisdom conventional or otherwise

But Professor Sackett and his colleagues have raised more important issues They cited studies conducted among Canadian storeworkers to support the conclusion that neither provision of care at the work site nor augmented educational effort enhance patient compliance or long term blood pressure control In the Canadian experiment a small fraction of an available male hypertensive population perhaps characterized by an aversion to medical care was randomly assigned to treatment by either an industrial physician or by each individual s family doctor Six months later compliance and blood pressure control in both settings were found to be appalling

We believe that these results may best be understood as reflecting the similarity of the fundamental therapeutic process Since no evidence was presented here to indicate that either community or industrial physicians were effective providers of antihypertensive care and in view of experience repeatedly reported in other conventional settings the dismal outcomes observed might have been expected Thus the impact of the physician patient interaction and not the alteration of the site of care remains the principal determinant of outcome

Promoting education (mastery learning sessions) in isolation from the fundamental therapeutic setting also failed to improve long term outcome The lack of success associated with these artificial and separate encounters should not however be offered as evidence that an educational process integrated within the structure of medical care would not be valuable

We contend that superior rates of compliance and blood pressure control achieved in our studies are the result of integrated patient education and facilitated access to treatment in a socially supportive environment (in this case the union) These factors are indeed the major components of the Gimbels program which also involves the use of a *protocol and* reliance on a health team Dissection and isolated evaluation of individual parts destroy the meaning of the whole and render assessment of the resulting segments irrelevant to the holistic scheme

The appropriate next step is to translate encouraging clinical results into a working hypothesis to be rigorously validated We question whether a *research design* in which individual patients are randomly allocated to alternate interventions is the appropriate model through which to evaluate the Gimbels project Indeed assignment of individual members of the whole group to alternate treatment approaches would inevitably mask the impact of peer support a factor deemed important to compliance Instead the methodology we are employing involves the allocation of comparable whole groups to alternate intervention strategies (e g Gimbels vs. Conventional Care) Two such studies are currently underway In one in order to determine the impact of physical accessibility on compliance our systematic treatment program is provided in on or off" site locations A second experiment involves screening at a number of sites and then allocating all hypertensive subjects at some locations to the on-site treatment program and at other locations referring

stenosis[2] and Marfan s syndrome[3] are transmitted as autosomal dominants Familial occurrence of congenital cardiovascular defects suggestive of a polygenic inheritance include hypoplastic left ventricle tetralogy of Fallot, and atrial septal defect[5] In some children the nature of the cardiovascular anomaly is predictable as part of a chromosomal abnormality or a constellation of defects representing a specific syndrome[7] and in others environmental factors are implicated the most documented being thalidomide and rubella virus

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Smoking and the cause of CHD

To the Editor

In regard to the Annotation of Dr P R J Burch (AM HEART J 93 805 1977) the findings of our epidemiological studies on the islands of Crete and Corfu should not distract from the great significance of smoking to CHD This could be disastrous during a period when such effort is being exercised against smoking

In our studies for the past almost 18 years among the farmers on the islands of Crete and Corfu the relationship between smoking and CHD was positive although not strong as in other studies. But one should not forget the fact that these populations are practically free of all other risk factors known today One can only assume with caution that smoking alone and in the amount and with the type of tobacco used in Crete and Corfu can be of less significance as a predisposing factor But as an additive factor to all other known risk factors it is much more destructive to the cardiovascular system

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REFERENCE

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Reply

To the Editor

The purpose of my Annotation was to consider how we might test etiological hypotheses of CHD bearing in mind that Correlation does not necessarily imply causation In passing I mentioned in connection with smoking a complication that arises at the outset because an earlier study had failed to demonstrate a *significant* correlation between smoking and CHD in several countries including Crete and Corfu Dr Aravanis is now able to tell us that among farmers on the islands of Crete and Corfu a positive but relatively weak association between smoking and CHD has been found after some 18 years of investigation Unfortunately his finding does not answer the question Does the association imply causation It merely adds to the list of countries in which such associations are found.

In my Annotation I pointed out that critical evidence capable in principle of answering the above question is furnished by studies of twins (especially MZ twins) that are discordant for smoking habits. Although the numbers available so far are too small for definitive conclusions they tend to support a constitutional (genetic) rather than a causal interpretation of the association. More recently I have analyzed the secular trends in sex specific and age-specific death rates from CHD in England and Wales, 1921 to 1973 and I find that the constitutional hypothesis is strongly supported Any causal action of smoking appears to be small or negligible

I can appreciate the concern of Dr Aravanis and others for the possibly destructive effects of smoking on the cardiovascular system It is of the utmost importance that medical scientists should establish, as objectively as possible whether or not such concern has a secure scientific foundation

In my view the critical evidence now available to us indicates that cigarette smoking can be largely or wholly exonerated as a *causal* factor in CHD

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More on BP measurement and cuff size

To the Editor

The review article on hypertension in children by Dr McLain makes many significant points calling attention to the necessity for more frequent determinations of blood pressure in children So many of his points are correct and well stated that I dislike to suggest a correction However since it is the American Heart Association Committee that made the error relative to blood pressure cuff size perhaps he will accept this suggestion.

The Committee on Blood Pressure Determination of the American Heart Association recommended in 1967 that a cuff for adults should be 20 per cent wider than the diameter of the limb This took into account the problems of obesity in adults and the erroneously high pressures that could be obtained if one used a cuff that was too small for an obese arm. Studies in adults have indicated very large errors using a standard 12 cm. adult cuff for seriously obese subjects In a normal non-obese adult population, Geddes and Whistler reported in a recent issue of AMERICAN HEART JOURNAL the effects of cuff width they found that a cuff that is too narrow overestimates and a cuff that is too wide underestimates blood pressure "

For some unexplained reason the Committee on Blood Pressure Determination recommended in 1967 that the size of the cuff for a child should be based on the *length* of the limb Obviously since there is no fixed relationship of the diameter of a limb to its length, this recommendation does not allow for a larger cuff size for an obese child nor as Dr McLain correctly pointed out will it allow for an appropriate width for the very large, muscular teen-ager It is not surprising then that an increasing number of reports are demonstrating an apparent relationship between obesity and hypertension

all hypertensive employees to care through *conventional* channels

In sum then while agreeing that the Hamilton experience substantiates the fact that neither augmented *education nor* facilitated access to care improve compliance *or outcome* when employed as isolated additions to conventional systems of care we contend that the value of these same elements as integral components of a comprehensive program remains to be demonstrated Hopefully experiments currently underway will establish the proper role of occupationally based system atic programs for the control of hypertension within the community

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Reply

To the Editor

Michael Alderman and his colleagues have carried out important pilot projects in hypertension control and we applaud their stand on toughening the scientific methods they will use to study their contention that strategies which have failed to improve compliance or blood pressure control in existing systems of care will do so when they are integral components of comprehensive care Indeed we suggest that the adoption of tougher science in the assessment of evidence would have prevented many of their disagreements with our work

For example they have characterized the rate of blood pressure control observed in our trials as appalling and dismal and that obtained in their own programs as "su perior The application of the tougher science we were advocating in our Annotation reveals that the results in Hamilton and New York are the same[1] The two studies simply defined satisfactory blood pressure control by different crite ria we required that patients (who started treatment with fifth phase diastolic pressures consistently ≥ 95 mm Hg) achieve a more rigorous blood pressure goal (< 90 mm Hg) whereas Dr Alderman s subjects (who started treatment with systolic values of ≥ 160 and/or fifth phase diastolic pressures ≥ 95 mm Hg and/or were already on hypotensive medica tion) were considered controlled if their blood pressure fell ≥ 10 per cent or below a less strict goal of 160/95 When compared by more compatible criteria (< 95 in Hamilton and < 160/95 in New York) the rates of control are 69 per cent and 66 per cent[1] Thus greater attention to the need for common criteria when comparing programs would have prevented their misinterpretation of the relative impacts of the two approaches.

A second example of the need for tougher science is seen in the failure to assess ancillary evidence concerning an infer ence Dr Alderman and his colleagues inferred that the hypertensives in our trial are perhaps characterized by an aversion to medical care yet the reference they cited also documented that 94 per cent of these same patients agreed not only to accept treatment but to enter a randomized trial of compliance improving strategies[2] Furthermore a review of other ancillary evidence reveals that the value of instructing patients about their illnesses and treatments has now been tested in ten controlled trials and the maneuver improved compliance in only one (two of these ten trials were random ized trials and both were negative) Finally an assessment of other more behaviorally oriented strategies will show that, even when applied in isolation or in the current health care system several (but not all) have been found successful in the randomized trials in which they have been tested

Vigorous debate over the validity transferability and generalizability of strategies for controlling blood pressure can make us better scientists and clinicians and should therefore be welcomed by investigators and fostered by journals as should methodologic discussions of issues such as the appro priate unit to be randomized in a clinical trial (for example in order to answer different questions we have randomized by individual patients families and whole practices and others have randomized by entire factories[3])

The key issue and the cardinal assertion in our Annotation is that strategies for achieving blood pressure control should no more be placed in general use without prior validation than should unproven drugs or untested surgery The criterion fo accepting or rejecting new evidence must be the scientific merit of the methods which produced it not the extent to which it concurs with the beholder s private or published views on the issue For this reason we were keenly disap pointed to learn that Dr Alderman and his colleagues will not randomize the firms or groups of patients to the alternative programs described in his letter but will decide which companies receive which interventions on other grounds As a result support for his important hypothesis will continue to rest on an uncertain foundation of sub-experimental evidence

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Book reviews

Clinical Vectorcardiography and Electrocardiography second edition By Jon D Cooksey M D Marvin Dunn M D and Edward Massie M D Chicago 1977 Year Book Medical Publishers, Inc 759 pages.

This second edition brings up to date the first edition published in 1960 18 years ago The authors have added new developments in the fields of electrocardiography and vector cardiography This is a textbook type publication The many chapters include anatomic considerations the dipole concept lead systems vector analysis vectorcardiographic reference frames the normal electrocardiogram ventricular gradient vectorcardiography and of course the electrocardiogram and vectorcardiogram in almost all the abnormal cardiac states The diagrams are simple and clearly reflect the authors approach and concepts of electrocardiography and vectorcardiography This is a good book that is not easy to read or study but it is well worth the effort however The great surge in interest in cardiology and in electrocardiographic monitoring requires a fundamental knowledge of electrocardiography and vectorcardiography to interpret properly the recordings Readers will find this to be a valuable source of material for study The book continues the high standards of the first edition

Cardiovascular Disease Continuing Education Review Joseph W Linhart M D, and Onkar S Narula M D Flushing, N Y 1977 Medical Examination Publishing Co Inc 135 pages. Price $12 00

Briefly this book contains 541 questions and referenced answers. Those preparing for their specialty board examinations in general internal medicine and cardiology will find this to be a good test of their knowledge of cardiology This book readily reveals the superiority of the essay type of examination over the current multiple choice questions in order to test the knowledge of a physician The questions and the narrative answers are well selected and practical in nature It is unfortunate that in order to keep the book small the answers to posed questions are brief but the reader will readily find the answers and can determine for himself how to extend the answers in greater detail This book in itself is good training Physicians will profit considerably by studying the book

Myocardial Failure Edited by G Riecker A. Weber and J Goodwin Co Edited by H D Bolte B Luderitz B E Strauer and E Erdmann, New York 1977 Springer Verlag 374 pages Price $22 10

This publication contains the papers presented at an international symposium held in Germany from June 17 through 19 1976 The three sessions were concerned with the molecular basis of myocardial function clinical aspects of myocardial failure and clinical pharmacology The many papers briefly review the problems of myocardial failure in an attempt to relate structural disturbances to functional impairment The action of drugs used in the treatment of congestive heart failure is discussed Those who have followed the literature closely will find little new in this publication whereas those who have not followed publications closely will find this paperback book to be an interesting review of the complex problems of congestive heart failure The presentations reflect very well the interest and opinions of many observers who have been concerned with congestive heart failure This is an interesting publication on a very important subject, congestive heart failure The approach has been concerned precisely with the myocardium itself The role of the peripheral circulation kidneys endocrine system and nervous system has been essentially ignored in the many brief papers Regardless it is the heart itself which was selected for discussion at this symposium.

Treatment of Cardiac Emergencies second edition By Emanuel Goldberger M D F.A C P St Louis 1977 The C V Mosby Company 391 pages. Price $16 50

This is the second edition of a useful book It should be placed in all emergency rooms and coronary care and intensive care units It is intended for the physician in practice The author describes the cardiac emergencies and presents their management in detail Dosage levels of potent drugs for example are carefully indicated The common and important cardiac emergencies are discussed all in such a manner that nurses will find the book comprehensible It is a well written useful up-to date book on an important subject in cardiology Goldberger is an experienced clinical cardiologist

As a pediatrician I am aware that we frequently demand special standards for children since they are not little adults However it is unreasonable to think that physical laws do not apply to children and the hard evidence is that the physical considerations that led to the adult recommendation of cuff width based on arm diameter should apply to children as well[5] It may be very well to frighten children and adults into weight reduction by labeling them as hypertensives but we should not confuse ourselves as to the real meaning of an elevated blood pressure in an obese patient when the cuff is too small

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Oral ISDN—long acting nitrite

To the Editor

In your issues of February and March 1977 Dr Prediman K Shah reviewed the role of vasodilators in acute and chronic cardiac conditions requiring ventricular unloading

I should like to comment on one point in these excellent papers referring to the use of oral isosorbide dinitrate (page 405)[6] The author mentions the lack of evidence for pharmacological activity of ISDN metabolites found in large amounts in the blood of dogs after oral administration of the compound

This is rather at variance with the clinically ascertained lasting hemodynamic improvement after oral ISDN intake despite rapid disappearance of the unaltered drug from the blood stream[1, 2]

The main ISDN metabolites (2 IS mononitrate and 5 IS mononitrate) have been isolated and used for clinical trials in humans by two independent research groups in Germany[3]

Both groups reported marked hemodynamic responses after adequate intravenous doses of the two mononitrates This pharmacological activity evidently accounts for the prolonged effect of orally taken ISDN and justifies its qualification as a long acting nitrite

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Clinical Vectorcardiography and Electrocardiography second edition By Jon D Cooksey MD Marvin Dunn MD and Edward Massie MD Chicago 1977 Year Book Medical Publishers Inc 759 pages.

This second edition brings up to date the first edition published in 1960 18 years ago The authors have added new developments in the fields of electrocardiography and vectorcardiography This is a textbook type publication The many chapters include anatomic considerations the dipole concept lead systems vector analysis vectorcardiographic reference frames the normal electrocardiogram ventricular gradient vectorcardiography and of course the electrocardiogram and vectorcardiogram in almost all the abnormal cardiac states The diagrams are simple and clearly reflect the authors approach and concepts of electrocardiography and vectorcardiography This is a good book that is not easy to read or study but it is well worth the effort however The great surge in interest in cardiology and in electrocardiographic monitoring requires a fundamental knowledge of electrocardiography and vectorcardiography to interpret properly the recordings Readers will find this to be a valuable source of material for study The book continues the high standards of the first edition

Cardiovascular Disease Continuing Education Review Joseph W Linhart MD, and Onkar S Narula MD Flushing NY 1977 Medical Examination Publishing Co Inc 135 pages. Price $12 00

Briefly this book contains 541 questions and referenced answers Those preparing for their specialty board examinations in general internal medicine and cardiology will find this to be a good test of their knowledge of cardiology This book readily reveals the superiority of the essay type of examination over the current multiple choice questions in order to test the knowledge of a physician The questions and the narrative answers are well selected and practical in nature It is unfortunate that in order to keep the book small the answers to posed questions are brief but the reader will readily find the answers and can determine for himself how to extend the answers in greater detail This book in itself is good training Physicians will profit considerably by studying the book.

Myocardial Failure Edited by G Riecker A Weber and J Goodwin Co Edited by H D Bolte B Luderitz B E Strauer and E Erdmann New York 1977 Springer Verlag 374 pages Price $22 10

This publication contains the papers presented at an international symposium held in Germany from June 17 through 19 1976 The three sessions were concerned with the molecular basis of myocardial function clinical aspects of myocardial failure and clinical pharmacology The many papers briefly review the problems of myocardial failure in an attempt to relate structural disturbances to functional impairment The action of drugs used in the treatment of congestive heart failure is discussed Those who have followed the literature closely will find little new in this publication whereas those who have not followed publications closely will find this paperback book to be an interesting review of the complex problems of congestive heart failure The presentations reflect very well the interest and opinions of many observers who have been concerned with congestive heart failure This is an interesting publication on a very important subject congestive heart failure The approach has been concerned precisely with the myocardium itself The role of the peripheral circulation kidneys endocrine system and nervous system has been essentially ignored in the many brief papers Regardless, it is the heart itself which was selected for discussion at this symposium

Treatment of Cardiac Emergencies second edition By Emanuel Goldberger MD FACP St Louis 1977 The C V Mosby Company 391 pages. Price $16 50

This is the second edition of a useful book. It should be placed in all emergency rooms and coronary care and intensive care units It is intended for the physician in practice The author describes the cardiac emergencies and presents their management in detail Dosage levels of potent drugs for example are carefully indicated The common and important cardiac emergencies are discussed all in such a manner that nurses will find the book comprehensible It is a well written useful up to-date book on an important subject in cardiology Goldberger is an experienced clinical cardiologist

Books received

Diabetes and the Heart By Samuel Zoneraich M D , Spring field, Ill. 1977 Charles C Thomas Publisher 275 pages Price $27 50

Clinical Electrocardiography A Simplified Approach By Ary Louis Goldberger and Emanuel Goldberger St Louis 1977 The C V Mosby Company 256 pages Price $9 95

Diabetes Mellitus B Edited by K Oberdisse Berlin 1977 Springer Verlag 1198 pages Price $215 60

Unit 1 Congestive Heart Failure By Rose Pinneo R N M S New York 1977 Appleton Century Crofts Inc 62 pages Price $4 50

Actualités Cardio Vasculaires Médico-Chirurgicales By R Froment P David A Gonin A Perrin P Michaud, and J Descotes Paris 1977, Editions Masson 176 pages

Progress In Lymphology Edited by R C Mayall and Marlys H Witte New York 1977 Plenum Publishing Corp 389 pages Price $39 50

Lipid Metabolism in Mammals vol 2 Edited by Fred Snyder New York 1977 Plenum Publishing Corp 376 pages Price $42 50

Announcements

Workshop on Thyroid Disease

A Workshop on Thyroid Disease sponsored by the American Thyroid Association will be held at the Copley Plaza Hotel Boston from November 5 through 7 1978 This two day program is designed for practicing physicians in internal medicine family practice and for surgeons and obstetricians who do not have subspeciality training in the field of thyroidology The workshop will emphasize practical approaches to clinical problems through a syllabus lectures small group discussions and self administered quizzes For program and registration information please write WT Registration Center for Continuing Education 1307 East 60th St Chicago Ill 60637 For additional information please contact the program chairman Dr P Reed Larsen Peter Bent Brigham Hospital 721 Huntington Ave Boston Mass. 02115

Workshop in Echocardiography

A Workshop in Echocardiography will be presented at the Don Cesar Beach Resort Hotel St Petersburg Beach Fla on January 25 through 28 1979 The workshop will be directed by Dr Louis Evan Teichholz Associate Chief of Cardiology Mt. Sinai Medical Center and Associate Professor of Medicine Mt Sinai School of Medicine New York For further information regarding this workshop please contact Ms Billie N Chiles Tampa Tracings P O Box 1245 Tarpon Springs FL 33589

American Heart Journal

October 1978 Volume 96 Number 4

Editorial

Population screening for myocardial ischemia

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The clinician does not usually become involved in the care of coronary heart disease (CHD) until myocardial injury is advanced and irreversible when angina or heart attack finally brings the patient to him By then the possibilities of salvage though real and important are not large—secondary prevention comes too late for most patients Clearly the long term goal is primary prevention but pending the desired mass changes in eating and smoking habits etc attempts to change the risk factors of individuals are effortful and not outstandingly effective Interest thus turns to a third preventive strategy intermediate between on the one hand primary prevention (instituted before recognizable myocardial injury) and on the other hand secondary prevention (usually following myocardial infarction) This intermediate strategy would start with population screening for signs of early myocardial ischemia What potential has such screening and can it lead to action that will effectively improve the prognosis? A recent report from England answers some of the questions whilst others remain frustratingly open

The Whitehall Study started with a simple screening examination of 18 403 male civil servants in London aged 40 to 64 years Early myocardial ischemia was defined on the basis of either (1) a positive response to a standardized and validated questionnaire on chest pain (the London School of Hygiene questionnaire in its self administered form²) or (2) a positive resting ECG (Q/QS S T segment or T wave items or left bundle branch block according to Minnesota Code criteria) The ECG comprised limb leads only and it was coded by specially trained and supervised technicians The whole examination therefore was speedy and cheap if it were adjudged useful acceptability and expense would be a small barrier to its widespread use

The first surprise from this study was that a self administered questionnaire was almost as effective as the ECG in predicting risk of CHD death each technique identified a group with about a fivefold increase in five year CHD mortality Either result carried a much greater predictive power than the familiar primary risk factors from which it was essentially independent Predictive power declined only slowly and for men with suspect ischemia the relative risk was still significantly elevated even in the fifth year of follow up The two indicators of ischemia (symptoms and ECG findings) showed rather little overlap and the most impressive prediction of risk came therefore from a combination of the two The men who by either criterion or both, had suspect ischemia (14 per cent of the whole examined population) included no less than half of all those who were to die from CHD in the ensuing five years

Clearly the traditional view is mistaken that heart attack commonly comes out of the blue

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Received for publication Oct. 21 1977

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To patient and doctor this may appear to be so, since earlier ECG changes and episodes of chest pain are usually transient, and either pass unnoticed or are soon forgotten But when one simple and crude examination can give advance warning of half the fatal attacks which will occur in the next five years, then clearly annual and perhaps more refined examinations could give warning of considerably more With annual checkups for myocardial ischemia, probably few major attacks would come unheralded—but would this lead to more effective preventive action, and how many false alarms would occur?

The most dangerous mistake for would be screeners is to believe that their activity is justified by the number of diagnoses they make In the Whitehall Study, despite the high relative risk and high proportion of deaths predicted, the absolute risk facing the man with suspect ischemia was nevertheless small Only about 1 per cent per year developed a fatal attack (London civil servants are a favored group in their low over all risk of CHD, and in an average American group of workers this risk might be somewhat higher) Here lies the first problem of screening for ischemia—if the criteria for a case are set wide enough to give warning of a high proportion of future heart attacks then only a small minority of the positive cases will actually encounter serious trouble in the next few years Stricter criteria can reduce false alarms but at the price of reducing also the amount of potential benefit to the community as a whole In the Whitehall Study a definition of ischemia requiring positive symptoms and ECG identified 0 6 per cent of men, whose five year CHD mortality rate was 15 per cent but it predicted only 8 per cent of the CHD deaths

On present evidence the chance of averting some of those 50 per cent of potentially predictable heart attacks is limited by our judgment on what treatment we feel would be acceptable to a man whose chances of surviving five years without our help are better than 90 per cent If we were in that position ourselves, would we wish to take long term antiarrhythmic therapy? Supposing that controlled trials in such a group were to have demonstrated some benefit, how large would that benefit need to be in order to justify instituting the treatment? Would five years of beta blockade have to save the lives of 1 in 100—or 5 in 100—or 10 in 100? My own instinctive feeling (I should not care to try and rationalize it) is that the first figure at least would be too low But even the second figure is out of range for a group whose five year mortality rate without treatment was only about 5 per cent The results of a trial of the prophylactic value of long term antiarrhythmic therapy in early myocardial ischemia would be intensely interesting, but one suspects that the entry criteria would need to ensure a risk without treatment somewhat higher than the 1 per cent per year of the Whitehall Study, and that would be a pity, because stricter entry criteria would exclude many men who are going to die of a heart attack

The Whitehall Study also produced challenging findings on the relation between myocardial ischemia and the main primary risk factors It might be expected that the importance of those factors well established in the stages preceding myocardial injury, would be much diminished once disease had got to this more advanced stage just as it is generally much diminished following myocardial infarction In fact, for blood pressure and plasma cholesterol concentration the predictive significance was as great in men with ischemia as in those without For overweight subjects there was a clear risk gradient in the ischemic group which was not evident in the remainder In the ischemic group mortality was higher among smokers than among non smokers, but the difference was less than in the remainder of the study group The results for leisure time activity were equivocal

In summary, it seems that the predictive force of the main modifiable risk factors remains unabated even at the relatively late stage of disease when there is already incipient ischemic injury Of course this does not mean that reduction of blood pressure, cholesterol, or weight at this stage would necessarily be beneficial That issue can only be tested by controlled trials But there need be less anxiety about intervention based simply on risk factor reduction than about long term use of drugs acting on the myocardium

It is a grievous thing to contemplate the possibility of mass screening for ischemia It involves telling men who thought they were well that their electrocardiogram shows abnormality or that minor symptoms may betoken heart disease rather than indigestion Such wilful trauma could only be justified if adequate trials had demon

strated a commensurate benefit from some treatment whether advice or drugs which could not otherwise have been instituted Such trials are much needed because they might lead to a strategy with considerable benefit to the community

All preventive trials are alarmingly large tedious and costly but trials of intermediate prevention because they would be conducted in relatively high risk groups would at least not need to be nearly so large as those of primary prevention Meanwhile screening for myocardial ischemia is certainly traumatic its benefits have not been demonstrated and its general use is not to be recommended except in research studies

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Clinical communications

Reproducibility of a consensus panel in the interpretation of coronary angiograms

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Coronary cineangiography is now generally accepted as the definitive procedure for the diagnosis of coronary artery disease Adequate assessment of coronary artery abnormality requires high quality angiograms and correct interpretation of films Angiographic interpretation should include an assessment of the severity and distribution of lesions coupled with judgement as to adequacy of the distal vascular bed

The most common method to evaluate distribution and severity of coronary lesions is joint review by *angiographer and surgeon with both* examining the films simultaneously Other methods are independent reading by two or more observers and a joint meeting to resolve disagreement[1] and review by a panel of experts [2] Lesion assessment by any method can be judged in the light of two interrelated criteria accuracy and consistency The criterion accuracy asks How truly does the evaluation reflect actual coronary morphology? Accuracy is influenced by all factors involved in production and interpretation of films, it is the most inclusive and valid single standard Accuracy of coronary angiography has been evaluated by comparing it to postmortem findings in several reports [3 5]

The second criterion consistency, evaluates a subset among the factors which contribute to accuracy and asks the question 'How reproducible is the interpretation of a single angiogram? This paper describes an evaluation of consistency of film reading by an expert panel There are two general ways by which films can be evaluated by a panel Panel members can render either *group opinion ' or ' consensus opinion* For group opinion, panel members read films independently and render separate estimates which are later averaged Zir and co workers[6] have evaluated the group opinion method as carried out by expert angiographers and report that *inter observer variability* is a significant limitation One cause of inter observer variability reported by Zir and colleagues was lack of uniformity in designation of the location of lesions For example when films were read independently one reader might assign a lesion to mid LAD and another assign the same lesion to proximal LAD This problem is minimized when all panelists review films simultaneously to render consensus opinion

For consensus opinion panelists review *films* simultaneously and arrive at a common judgement A consensus panel comprised of a senior radiologist and cardiologist plus a second year cardiac fellow was used to provide a standard to judge the performance of independent film readers by DeRouen and co workers [7] It was found that the number of angiograms interpreted by individual readers in the preceding year was significantly and positively associated with agree-

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Supported by NHLBI Specialized Center of Research in Arteriosclerosis Grant No HL 14138

Received for publication Sept 1 1977

Accepted for publication Nov 7 1977

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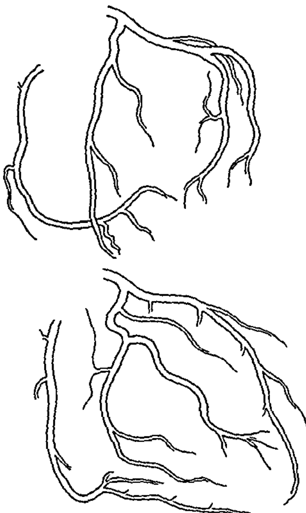


Fig 1 Blank sketch of the coronary tree in LAO (top) and RAO (bottom) views Patient's initials are shown in upper right.

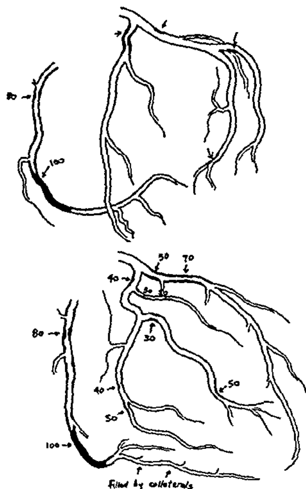


Fig 2 Record of panel consensus in patient E N

ment with the panel The length of experience in practice and whether or not they were certified in cardiology did not influence the degree to which individual readers agreed with the panel DeRouen and co workers did not evaluate the consistency of performance of their reference panel but accepted a single consensus opinion as a standard

We recently convened a consensus panel of four expert angiographers to assess change in coronary angiograms for a pilot study of medical therapy in patients with premature atherosclerosis We randomly selected fourteen films for duplicate reading to determine the consistency of consensus panel opinion

Materials and methods

Coronary angiography was performed by the Judkins technique by one angiographer (M E S) Angiograms were recorded at 60 frames per second on 35 mm Shellburst film utilizing a General Electric 6 inch cesium iodide image intensifier with overframing In all patients the left coronary artery was recorded in at least five views and the right coronary artery in at least three Films were projected on a Tage Arno projector and were viewed simultaneously by the panel.

In all the panel evaluated films of 38 men ages 40 to 51 years with premature atherosclerosis manifest by myocardial infarction These patients participated in a clinical trial to evaluate the effect of risk factors on the natural history of coronary artery disease During the clinical study each patient had had two coronary angio

Table I Panel assessment of coronary obstruction Maximum per cent stenosis within each vessel segment

Patient	Panel session	LM*	LAD_1	LAD_2	LAD_3	D_1	D_2	CX_1	CX_2	OM	PL	R_1	R_2	P_1	PD	IWB
R B	1	90	60	85	75	75	0	75	0	0	0	100	DTO†	DTO	DTO	DTO
	2	27	50	85	75	80	0	75	40	0	0	100	DTO	DTO	DTO	DTO
R B	1	0	0	50	20	0	0	60	50	30	0	75	0	50	0	0
	2	0	0	40	0	0	0	65	65	50	0	70	0	50	0	0
G B	1	0	50	100	DTO	100	0	0	0	75	0	100	DTO	DTO	0	0
	2	0	60	100	DTO	100	0	0	0	80	0	100	DTO	DTO	50	0
V G	1	40	30	60	50	50	0	60	90	0	50	80	100	90	DTO	DTO
	2	30	50	70	0	0	0	30	90	35	0	80	100	90	DTO	DTO
A L	1	0	75	0	40	0	0	0	75	0	100	20	0	0	75	65
	2	0	70	0	0	0	0	0	85	30	100	25	0	0	[illegible]	50
S M	1	0	30	100	DTO	60	0	50	90	60	50	75	50	75	50	0
	2	0	20	100	DTO	70	0	50	90	70	70	75	50	75	60	0
E N	1	0	50	70	0	0	0	40	40	30	50	80	100	DTO	DTO	DTO
	2	0	60	75	0	0	0	40	50	60	30	90	100	DTO	DTO	DTO
R P	1	20	90	0	40	0	0	70	40	80	0	100	DTO	DTO	DTO	DTO
	2	30	90	0	50	0	0	75	50	50	0	100	DTO	DTO	DTO	DTO
D R	1	0	75	0	0	0	0	40	0	60	0	0	20	0	0	0
	2	0	80	0	0	100	0	50	0	60	0	0	20	0	0	0
G S	1	0	40	80	30	50	0	50	0	50	0	50	100	DTO	DTO	85
	2	0	50	80	30	0	0	70	0	60	0	55	100	DTO	DTO	80
S S	1	0	0	40	30	0	0	50	0	0	0	70	70	95	0	0
	2	0	0	40	0	0	0	40	0	0	0	75	75	95	0	0
I S	1	0	75	60	0	70	0	0	0	70	0	100	DTO	DTO	DTO	DTO
	2	75	75	75	0	75	0	0	0	75	0	100	DTO	DTO	DTO	DTO
R W	1	30	95	50	0	0	0	0	75	70	0	50	50	70	0	100
	2	0	95	55	0	0	0	0	75	75	0	55	55	60	0	100
C W	1	40	50	50	0	60	70	40	0	0	0	70	100	DTO	80	60
	2	30	30	40	0	35	75	50	0	0	0	75	100	DTO	90	0

Segment abbreviations are LM = left main LAD = left anterior descending D = diagonals CX = circumflex OM = obtuse marginal, PL = posterolateral R = right coronary artery PD = posterior descending IWB = inferior wall branches (See Ref 7 for further detail)
†Distal to occlusion segment not evaluated

grams and as part of the panel review process serial films were evaluated for change, but findings regarding this change will not be reported here This report deals only with the consistency of an expert panel and presents a comparison of stenosis estimates derived from the same films on two occasions

The panel was convened for two sessions each lasting two consecutive days In August 1975 the panel evaluated 25 films in March, 1976, the panel evaluated 13 new films and 14 films selected at random from those of the preceding August At the March session the panel was informed that an undesignated number of August films would be intermixed at random with new films Seven months had elapsed between sessions and we feel that duplicate panel assessments can be considered independent of each other The panel members were

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Melvin P Judkins M D Professor and Chairman Department of Radiology Loma Linda University School of Medicine,

George G Rowe M D , Professor of Medicine University of Wisconsin School of Medicine,

Ronald H Selvester M D , Professor of Medicine University of Southern California School of Medicine

The procedure for film reading was as follows While the film was being mounted for projection each panel member was provided an identical outline of the coronary tree to be reviewed These coronary sketches displayed a blank outline of the RAO and LAO views of each individual patient s coronary arteries (Fig 1) Panel members had no clinical data regarding patients except knowledge that all were men with proven

myocardial infarction at an early age All angiograms had been exposed to show coronary artery views in the same sequence LCA injection 60 LAO 30 LAO 15 RAO 30° RAO and 5 RAO RCA injection 60° LAO 30 LAO and 30° RAO A technician advanced the film past all identifying data to the first coronary sequence before panel members viewed a film Panel members sat around the projector and one panelist in rotation operated the projector Each panelist working independently sketched and reported stenosis estimates on the diagrams without revealing these to other panel members Films were next replayed and discussed openly by the panel to arrive at a consensus estimate of the degree and location of all stenotic lesions During the open discussion individual graders could change their previously recorded diagram and frequently did so as a result their readings were no longer independent precluding group opinion analysis Consensus estimates were dictated by the panel to a physician (M E S) who diagramed them on a separate record (Fig 2) When a panel consensus had been recorded panel members turned in their individual diagrams and adjourned to another location while the technician mounted a new film The average time required by the panel to review a single film by this method was approximately 30 minutes

To provide common units of information for data analysis each consensus diagram was divided into segments according to the reporting system suggested by the American Heart Association Ad Hoc Committee for Grading Coronary Artery Disease This was modified to include inferior wall branches of the right coronary artery distal to the crux

Consensus estimates of stenosis ranged from zero (no luminal narrowing) to 100 per cent (complete obstruction) and were based on the maximum narrowing seen in any projection Data analysis was done by vessel site and quantified the difference between first and second grading sessions There were 15 possible sites in each of the 14 patients Among the 210 possible sites 186 were evaluated Vessel sites which were not graded were those distal to complete obstruction A significant lesion was defined as stenosis equal to or greater than 70 per cent stenosis (reduction in cross sectional area)

Panel consistency was analyzed three ways First for consistency in designating the presence

Table II Measures of dispersion between the first and second panel readings for per cent of stenosis

Coronary artery segment	*Number observed*	*Per cent agreement presence of ≥ 70% stenosis*	*Per cent having readings deviate by 20% or more*	*Standard deviation of differences*
LM	14	86	21 4	24.8
LAD	14	100	14 3	7 0
LAD	14	86	0 0	5 ?
LAD	12	100	33 3	18 1
D	14	86	28 6	29 7
D	14	100	0 0	1 3
CX	14	93	14 3	9 1
CX	14	100	7 1	11 1
OM	14	93	35 7	13 3
PL	14	93	21 4	14 5
R	14	100	0 0	3 2
R	10	100	0 0	2 1
R	7	86	0 0	3 8
PD	8	100	1? 5	17 3
IWB	9	100	0 0	6 5
Weighted Averages		94 6	13 44	14 14

Segment abbreviations are as given in Table I

or absence of a significant lesion in each segment Next the degree of disagreement was computed by the number of sites with duplicate readings which differed by 20 per cent or more Third the standard deviation of the difference between readings was obtained for each site

Results

Table I shows the per cent stenosis assessed by the panel for each lesion site for each patient for the two grading sessions Sites which could not be graded (distal to complete occlusions) are designated DTO Pairwise t tests were done for the session differences for each lesion site and none were significantly different from zero This indicates that the panel did not exhibit a measureable tendency to increase or decrease stenosis estimates between the two sessions Over all average stenosis estimates on the second session was less than 0 6 per cent higher than at the first session

There was good agreement between the sessions regarding the presence or absence of a significant lesion with only ten discrepant readings Agreement therefore for all 186 lesion sites was 94 6 per cent as shown in Table II as a

weighted average Somewhat less consistency was observed in small vessels, for example mid LAD first diagonal and distal right, which showed 86 per cent agreement It should be noted that the difference between significant and not significant might represent a difference between 60 per cent and 70 per cent stenosis and, indeed, that was the case in four out of ten discrepant readings An important exception was the magnitude of the discrepancies in the left main segment in two of the 14 patients These are discussed individually later

Table II shows two additional measures of dispersion between the first and second panel readings The next measure is the per cent of patients for whom a given vessel site had stenosis readings which deviated by 20 per cent or more between the two grading sessions Among major coronary vessels the right coronary artery in all three segments showed the greatest consistency by this measure and all grades from the first session were within 20 per cent of grades from the second sessions The proximal LAD and circumflex also showed excellent agreement In minor vessels the disagreement ranged from 0 (D) to 36 per cent (OM) In the case of the second diagonal branch the excellent agreement may be explained in part by the high proportion of 0 per cent and 100 per cent stenosis because these extremes conceptually invite consistent readings However the first diagonal branch of patient D R which filled faintly through collaterals was graded 0 per cent stenosis at the first session and 100 per cent at the second session

The vessels showing most grading inconsistencies by this method were the obtuse marginal branch the distal segment of the left anterior descending and the first diagonal branch Considering all 186 vessel segments, 25 (13 44 per cent) were discrepant by 20 per cent or more at the two panel sessions (see Table II) Every patient in the series had at least one vessel site with a discrepant reading of 20 per cent or more One patient V G, had six such discrepancies Of the 25 discrepancies, 16 (64 per cent) may be considered hemodynamically insignificant since they deal with noncritical lesions by conventional standards according to both panel readings

The third measure of dispersion in Table II is the standard deviation of the difference of the two readings for each vessel site The standard deviation may be regarded as the better measure of consistency since it utilizes all discrepancies and gives considerable weight to the larger ones. A weighted average* of the standard deviations for all sites yields an over all variability of 14 1 per cent The greatest standard deviations were observed for the first diagonal branch (30 per cent) and the left main segment (25 per cent)

Discussion

It appears from this study that a panel of expert angiographers has a consistency of 95 per cent when rendering consensus opinion with respect to the presence or absence of a significant lesion (≳ 70 per cent stenosis) Significant stenosis has been variously defined in previous reports of angiographic precision as 70 per cent "lumen reduction or 50 per cent "diameter" reduction Since these two measurements are equivalent we adopt the 70 per cent convention However, it is important to point out that this degree of agreement may be overstated since it compresses all possible degrees of coronary abnormality into two classes significant and nonsignificant Compression to this extent severely limits the use of coronary angiography for description of the natural history of ischemic heart disease or stratification of patients for clinical therapy trials

This is the only report in which a panel had been asked to provide duplicate readings of the same coronary angiogram at two different sessions Therefore the estimate of panel consistency is not directly comparable to previous reports[2,6,8] Our results however, do seem somewhat better than the agreement between panel members rendering "group opinion reported by Zir and co workers[6]

To study the natural history of coronary disease or stratify patients for clinical trial a more useful estimate of panel performance can be derived from the raw data and standard deviations presented in Table II These standard deviations indicate that a consensus panel appears adequate for evaluation of the right coronary artery, proximal and mid left anterior descending coronary artery, and circumflex where standard deviation of duplicate stenosis estimates do not exceed 10 per cent In the left main coronary segment and diagonal and marginal branches the

*Weighted average = $\left(\frac{\Sigma (N-1) SD}{\Sigma (N-1)}\right)^{1/2}$

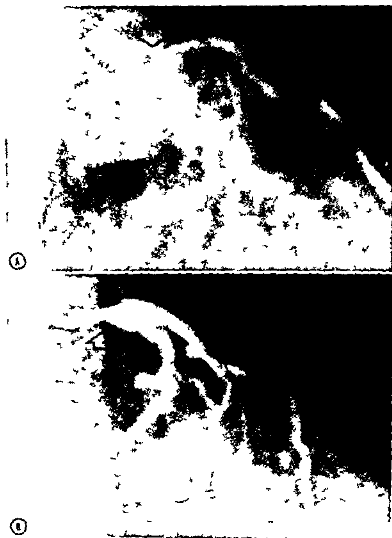


Fig 3 A and B Two examples of left main segments with major discrepancies in panel consistency A patient R B B patient I S See text for discussion

standard deviation of duplicate stenosis estimates ranged from 15 to 30 per cent In these vessels panel reading could usefully be augmented by one of several additional reading procedures described later

It has been suggested that one factor which may influence observer variability is the number of positive findings There will be better agreement in those vessels with no lesion or complete stenosis In our study this appears to be the case in the second diagonal branch which was free of disease in all but one patient On the other hand it is to be noted that the proximal and mid left anterior descending and right coronary artery show good reproducibility with 36 43 and 57 per cent positive findings Good agreement in these segments is in keeping with the previous reports of Zir and co workers[4] and Detre and colleagues[6]

Despite the over all encouraging results reported here we must emphasize the problem we have encountered in stenosis estimates of left main coronary segment In two of the 14 cases the left main segment was considered without significant disease at one time and severely stenotic at another time Since significant left main lesions pose a very special problem because of their prognosis[9,12] discussion of these two patients is pertinent Fig 3A shows a frame of proximal left coronary artery on patient R B During the first review it was agreed by the members of the panel that he had a 90 per cent

narrowing of the left main On the second review, the panel members spent approximately 45 minutes trying to decide on whether there was a left main lesion or if there were two separate ostia for the LAD and circumflex According to the second view the finding could be explained by a jet from the tip of the catheter filling both ostia and appearing to be a stenotic lesion After considerable discussion they did not reach an agreement, readings varied from 0 to 80 per cent stenosis (average 27 per cent) The second patient with a discrepant left main lesion was I S Fig 3B illustrates a frame of the coronary angiogram On the second review the panel decided there was 75 per cent ostial stenosis, in their first review the left main was read as normal

We are not the first to encounter difficulty in evaluating left main lesions In the left main coronary artery, Zir and co workers[6] found disagreement among the four observers in three of the 20 angiograms (15 per cent) While our methods are not directly comparable our results are very similar since the disagreement of our panel with itself was two out of 14 or 14 per cent Improved stenosis estimation is clearly desirable because of the importance of this segment in the genesis of massive myocardial infarction and sudden cardiac death We feel that the problem presented by the left main coronary segment has two elements First, there is a need for different or improved imaging procedures to provide multiple views, and second, there is need for improved reading procedures The case illustrated in Fig 3A appears to require an improved or different imaging procedure with multiple views, and will not be remedied by improved reading techniques alone The problem illustrated in Fig 3B could be alleviated by improved film reading procedures With human readers either individual or panel members, it seems important to employ film reading schedules which reduce reader fatigue while requiring the systematic examination of all segments Systematic reading is particularly important when multiple segments are involved and there are some lesions present which tend to attract the reader s attention to the exclusion of others An alternative approach could be to augment human reading with automated stenosis estimates of all coronary segments The quantitative procedure described by Brown and associates[13] which requires that a reader trace the coronary arteries has been shown feasible An instrumental procedure with less potential for human error since it provides for automatic vessel edge finding, has been described by Selzer and coworkers[14] Routine acquisition of quantitative data on all segments could extend the scope of coronary angiographic interpretation and assist in quality control

Summary

This report describes the consistency of coronary angiogram evaluation by a four man panel of experts rendering 'consensus opinion" The panel evaluated films from 38 patients at two grading sessions separated by an interval of seven months Fourteen patients' films were selected at random for duplicate evaluation These contained 186 lesion sites The panel was 95 per cent consistent in designating significant stenosis (≥ 70 per cent) Consensus' panel reading appears more consistent than group opinion panel reading The over all standard deviation of the difference in panel reading was 14 per cent The panel was most consistent in evaluating the right coronary artery, proximal LAD, and proximal circumflex In the left main segment two of fourteen duplicate evaluations showed major discrepancy

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Coronary artery fistulas emptying into left heart chambers

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A coronary artery fistula is an uncommon congenital anomaly [1] The majority of these fistulas empty into the right heart chambers In a review of two hundred cases of coronary fistulas, only 17 entered the left heart In 2,300 patients studied with selective coronary arteriography in our laboratory, three patients had coronary artery fistulas which emptied into the left side of the heart

Case 1

B P was a 27 year old white female school teacher who was admitted to the Buffalo General Hospital for evaluation of heart murmur and recurrent atrial fibrillation She had a febrile illness diagnosed as 'acute rheumatic fever' at age 7 for which she was hospitalized for 3 months Subsequently she was well until 3 years before admission when she began to have recurrent episodes of palpitation On April 17 1972 she had a severe episode of palpitation for which she went to the emergency room of another hospital and was noted to have atrial fibrillation with rapid ventricular response The rhythm was converted to sinus electrically and she was started on digoxin and quinidine One week before admission she had another episode of atrial fibrillation which ceased spontaneously She denied symptoms of congestive heart failure

Physical examination disclosed a well developed obese white female The pulse was 80 per minute and regular, and the blood pressure was 150/40 mm Hg Carotid pulses were bounding The first heart sound was normal A Grade 3/6 continuous murmur with a predominant diastolic component was heard over the entire precordium with maximal intensity over the third left intercostal space A third heart sound was audible at the apex Examination otherwise was within normal limits The electrocardiogram showed notched P waves in Leads I and II suggestive of left atrial enlargement The chest x ray showed cardiomegaly with evidence of left atrial and left ventricular enlargement

Catheterization of the right and left heart was performed Pressures in the right side of the heart were normal The left atrial pressure measured by the transseptal technique was also normal Simultaneous pressures in the left atrium and left ventricle showed a small (2 mm Hg) pressure difference between the left atrium and left ventricle during the rapid filling period of the left ventricle and again at the end of ventricular diastole during the left atrial contraction The left ventricular pressure was normal and the aortic pressure showed a wide pulse pressure (130/60 mm Hg)

Cineangiograms following injection of contrast into the left atrium showed enlargement of the left atrium and a normal appearance of the mitral

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Supported in part by Program Project Grant HL 15194 from the National Heart Lung and Blood Institute and in part by contributions to the Buffalo General Hospital in memory of Cecil Kisiel

Received for publication Sept 9 1977

Accepted for publication Jan 13 1978

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valve Left ventriculograms showed enlargement of the left ventricle with an end diastolic volume of 343 ml and an ejection fraction of 62 per cent There was neither evidence of aortic regurgitation nor evidence of left to right shunt

Aortic root cineangiograms showed aneurysmal dilatation of the left sinus of Valsalva The main left coronary artery was markedly dilated (about 1 cm in diameter) A large fistula was derived from the left coronary artery and was directed superiorly and medially before it connected with the left atrium

Fig 1 shows frontal projections of the left coronary arteriogram made with 32 ml of Renografin and serial cut films at a rate of 4/second for 2 seconds In Fig 1A the main left coronary artery is markedly dilated and appears aneurysmal in its distal portion There is light opacification of the left atrium Fig 1B is the next frame of the arteriogram shown in Fig 1A The fistula now is visualized and the left atrium shows dense opacification

Open heart surgery was performed on July 9 1973 at the Texas Heart Institute by Dr Denton Cooley Exploration revealed that she had an anomalous branch of the left circumflex coronary artery which had a fistulous communication with the left atrium The left coronary artery was greatly dilated and almost aneurysmal at its nearest termination at the fistula site The left atrium was opened and the ostium of the fistula was found above the mitral valve and adjacent to the base of the auricular appendage The fistula was oversewn at that point The coronary artery was dissected out carefully preserving the circumflex and left anterior descending branches The coronary artery was ligated at the appropriate point and the anomalous artery was then obliterated with sutures Her postoperative course was uneventful except for the development of atrial fibrillation on the fifth postoperative day which was converted to sinus rhythm with quinidine Disappearance of the murmur and atrial fibrillation and decreased heart size were noted following surgery

Case 2

J Q was a 65 year old white man with a history of acute rheumatic fever at the age of 20 Involvement of the mitral valve was noted at age 25 He had been seen periodically by one of us (D G G) since 1958 with the diagnosis of mitral



Fig 1 A and B A Frontal projection of the left coronary arteriogram during power injection of 32 ml of Renografin into the left coronary artery The left main coronary artery is markedly dilated and its distal portion appears aneurysmal There is light opacification of the left atrium *MLC* = main left coronary artery *LA* = left atrium *B* Next frame of the arteriogram shown in *1A* The fistula is now opacified and directed superiorly and medially connecting with the left atrium Note dense opacification of a large left atrium through the fistula Abbreviations as in *1A* *F* = fistula

stenosis and regurgitation He had had intermittent episodes of atrial fibrillation for which he was treated with digitalis and quinidine He had good exercise tolerance until October 1972 when he developed increasing fatigue dyspnea and orthopnea Physical examination revealed a blood pressure of 170/90 mm Hg a regular pulse of 70 per minute normal jugular venous pressure and a loud first heart sound An opening snap a Grade 3/6 diastolic rumble and a Grade 2/6 pansystolic murmur were heard at the apex The chest x ray showed left atrial enlargement slight left ventricular enlargement and pulmonary

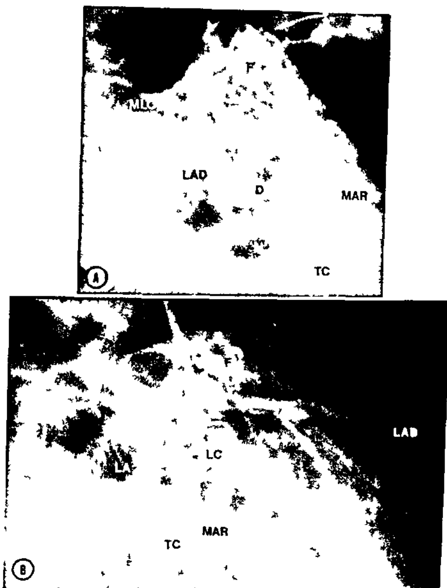


Fig 2 A and B *A* Left anterior oblique view of the left coronary arteriogram using cut film demonstrates a round angiomatous plexus The origin of the fistula from the proximal left circumflex artery and its connection with the left atrium were clearly seen by cineangiography Abbreviations as *Fig 1* *LAD* = left anterior descending artery *MAR* = marginal branch of left circumflex artery *TC* = terminal circumflex artery *D* = diagonal branch of the left anterior descending artery *B* Right anterior oblique projection of the left coronary arteriogram shows the fistula and contrast in the left atrium Abbreviations as in *Figs 1* and *2A*

venous congestion The electrocardiogram showed first degree atrioventricular block left anterior hemiblock, and digitalis effect

On April 20, 1973 right and left heart catheterizations and angiography were performed The pulmonary wedge pressure was 25 mm Hg the pulmonary artery pressure was 40/12 mm Hg and there was an 18 mm Hg gradient across the mitral valve The left ventricular pressure was normal Left ventriculography showed minimal mitral regurgitation Visualization of the left heart following injection of the contrast into the pulmonary artery showed left atrial enlargement The mitral valve appeared thickened and bulged down during diastole in a manner typical of mitral stenosis

The right coronary arteriogram showed mild stenosis of this artery shortly before the origin of the posterior descending branch The left coronary arteriogram showed a main left coronary artery and left anterior descending which appeared normal The left circumflex artery showed no evidence of an occlusive lesion However, about a centimeter from its origin it gave rise to a branch which was the arterial supply of a hemangioma about 2 5 cm in diameter which emptied into the left atrium (see Fig 2)

Cardiac output and estimation of flow through fistula Cardiac output was done by dissolved hydrogen technique using left ventricular infusion and aortic sampling [3] and measured 5 81 L/minute For the estimation of shunt flow isotonic

saline containing a known amount of dissolved hydrogen was infused directly into the left coronary artery at a rate of 7.2 ml per minute. Left ventricular samples were drawn between two to four minutes of the infusion and analyzed for hydrogen. The amount of infused hydrogen recovered in the left ventricle was calculated as the product of average left ventricular hydrogen concentration and cardiac output. This product was then expressed as a fraction of hydrogen input (hydrogen concentration in infusate × 7.2 ml/minute). Since hydrogen traversing the normal coronary circulation is eliminated essentially completely in the lungs, the fraction of infused hydrogen recovered in the left ventricle represents the fraction of the left coronary inflow passing through the fistula. Flow through the fistula calculated in this manner was 69 per cent of the left coronary inflow.

Exploration during mitral commissurotomy by Dr Thomas Z. Lajos revealed three small orifices in the left atrium. The fistulas were oversewn at these points.

Case 3

J. B., a 44 year old black female school teacher was hospitalized for evaluation of chest pain and dyspnea of 9 months duration. These symptoms usually occurred with exertion and were relieved after about 5 minutes of rest. Chest x ray shortly after the onset of symptoms showed an enlarged heart. The patient was placed on digoxin 0.25 mgm daily without improvement. Physical examination revealed a blood pressure of 150/80 mm Hg. The pulse was 72 per minute and regular. The heart sounds were normal. A Grade 2/6 systolic ejection murmur was heard along the left sternal border. The chest x ray showed left ventricular enlargement. The electrocardiogram showed left anterior hemiblock and voltage criteria for left ventricular hypertrophy.

On April 25, 1973, left heart catheterization and coronary arteriograms were done. Left ventricular and aortic pressures were normal and there was no gradient across the aortic valve. The right coronary artery and circumflex branch of the left coronary artery were small and appeared normal. The left anterior descending branch of the left coronary artery was markedly enlarged. A small anomalous branch derived from the anterior descending in its distal portion connected directly with the ventricle.

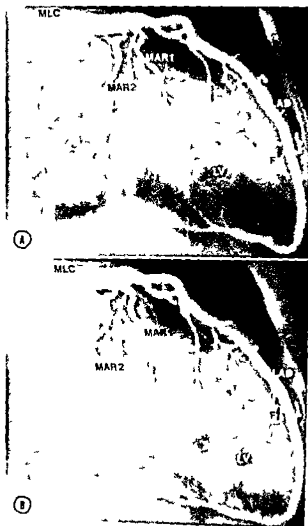


Fig. 3. A and B. *A*, Right anterior oblique view of the left coronary arteriogram shows enlargement of the left anterior descending artery and a fistula of small caliber *(arrow)* joining the left anterior descending artery with the left ventricle. Note contrast bursting into the left ventricle. Abbreviations as in *Figs. 1* and *2*. LV = left ventricle. *B*, Later frame of the arteriogram seen in *3A*. The fistula now shows smaller caliber and the contrast filled left ventricular cavity is outlined. Abbreviations as in *3A*.

Fig. *3A* is a right anterior oblique projection of the left coronary arteriogram using cut film showing a small fistula emptying into the left ventricle.

Fig. *3B* is a later frame of the same large film sequence showing opacification of the entire left ventricular cavity through the fistulous communication.

By using hydrogen as a tracer as described in Case 2, cardiac output measured 4.72 L/minute and shunt flow through the fistula was 38 per

cent of the left coronary inflow.*† This patient was not operated on and her symptoms have remained unchanged.

Discussion

With advances in selective coronary arteriography and coronary surgery, diagnosis and correction of coronary fistulas are done more frequently. Coronary arteriography is especially helpful in diagnosing fistulas without clinical manifestation or those involving multiple vessels or recipient chambers. The fistula originates most frequently from the right coronary artery. The most common recipient chambers in order of frequency are the right ventricle, the right atrium, and the pulmonary artery.[4] Oldham and colleagues reported 12 cases of coronary fistulas and reviewed 188 published cases.[1, 3, 13] The fistula emptied into the left atrium in only 12 of their 200 cases. Two other cases have been published.[14, 15] Reddy and colleagues[16] reported a case of coronary fistula to the left ventricle and reviewed nine previous cases. We have found eight additonal reported cases.[1, 24] Therefore to our knowledge 32 cases of fistula emptying into the left heart have been published. Symptoms of congestive heart failure, angina pectoris, bacterial endocarditis, and frequent upper respiratory tract infections are usually seen in these patients. Atrial fibrillation is commonly found in older patients and may precipitate congestive heart failure.[4]

In our first patient recurrent atrial fibrillation was the presenting symptom although she was only 27 years old. Findings of a continuous murmur, a wide arterial pulse pressure and enlargement of the left atrium and left ventricle were similar to those with patent ductus arteriosus. The loud diastolic component of the murmur and the absence of increased pulmonary vascularity, however, were not compatible with this lesion.[4] Dilatation and overload of the left atrium by a large shunt through the fistula appeared to be responsible for the arrhythmia and this mechanism was confirmed by cessation of the atrial fibrillation and decreased heart size after surgery. In the second patient the symptoms could be explained by mitral valve disease. However since he was 65 years old and the left ventriculogram showed impairment of contractility, coronary arteriography was done prior to mitral commissurotomy and to our surprise a fistula from the left coronary artery to the left atrium was discovered. The flow through this fistula was found to be about two thirds of the left coronary inflow. Whether there is any relation between the fistula and left ventricular dysfunction is not clear. Our third patient had dyspnea and atypical angina pectoris and had no signs related to the fistula except a non specific systolic murmur.

Coronary fistulas to the left ventricle are usually associated with a continuous[3] or only a diastolic murmur. Closure of the fistulous communication during ventricular systole accounts for the absence of a systolic component in some patients. Cases without a heart murmur have also been reported.[16, 5] Coronary arteriography in our patient revealed enlargement of the left anterior descending artery, presumably due to increased flow through this artery and "run off" to the left ventricle. Left ventriculography showed hypokinesis of the anterior wall. Calculation of the shunt through the fistula by the method described earlier showed that about one third of the left coronary inflow entered the left ventricle through the fistula. Myocardial ischemia is an uncommon manifestation of coronary artery fistula. It is postulated that blood is shunted away from the coronary circulation causing a decreased pressure gradient across the myocardial capillaries. This hypothesis could explain both chest pain and hypokinesis of the anterior wall of the left ventricle in this patient with left coronary-left ventricular fistula. Using hydrogen dissolved in saline as tracer, we were able to estimate the shunt flow in the second and third patients. In the first patient this method of shunt flow measurement did not seem applicable. Since the fistula had a short conduit and a large flow, a large amount of hydrogen which had entered the left heart through the fistula would recirculate into the left coronary artery.

Summary

We present three cases of coronary artery fistulas entering into the left heart chambers. Coronary arteriography in one showed aneurys

*Because of the left to-left shunt a small amount of hydrogen entered the left ventricle from shunt outflow in addition to the large amount of hydrogen infused, thus the value of cardiac output probably underestimates actual cardiac output by 5 to 15 per cent.

†Reflux of the solution containing hydrogen from the left main coronary into the aorta appeared unlikely because of the following reasons: (1) Left main coronary arteries were not short in these patients and the catheter tips were in satisfactory positions in the main left coronary arteries. (2) Hydrogen dissolved in saline was injected at a low rate of 7.2 mL/min. Any reflux which occurred would cause the calculation of coronary blood flow to be too low.

mal dilatation of the main left coronary artery and a fistulous communication with a large left atrium Exploration during repair revealed an anomalous branch of the left circumflex emptying into the left atrium In the second case the proximal left circumflex gave rise to a branch supplying a hemangioma which emptied into the left atrium Coronary arteriograms of the third patient showed an enlarged left anterior descending artery with an anomalous branch emptying into the left ventricle Shunt flow was estimated with hydrogen as a tracer in the last two cases and was two thirds and one third of the left coronary inflow respectively Review of the literature shows 32 previously reported cases of a fistula draining into the left side of the heart

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Arterial hypoxemia following the administration of sublingual nitroglycerin

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It is our policy to administer sublingual nitroglycerin 10 to 15 minutes before induction of anesthesia in patients about to undergo coronary artery bypass surgery Routine blood gas determinations, after the administration of nitroglycerin and before the induction of anesthesia, revealed that some patients had surprisingly low arterial PO_2 (PaO_2) values We, therefore, decided to study the effect of nitroglycerin on arterial blood gases and hemodynamics in a group of these patients Our results demonstrate that PaO falls significantly following the administration of sublingual nitroglycerin to patients with coronary artery disease breathing room air The possible mechanisms and clinical implications are discussed

Materials and methods

Seventeen men and four women 38 to 61 years of age, were studied Each had experienced typical stable exertional angina for at least six months Coronary angiography revealed that each had one or more high grade obstructive lesions There was no evidence of congestive heart failure or valvular disease in any of these patients All medications except nitroglycerin had been discontinued 48 hours prior to coronary artery bypass surgery

Blood gas determinations were done before and after nitroglycerin in a total of 21 patients They were divided into two groups Group I consisted of 13 patients who had received morphine (10 to 15 mgm) scopolamine (0 4 to 0 5 mgm) premedication intramuscularly, approximately 60 minutes before the studies Both blood gas and hemodynamic studies were done in this group Group II in eight unpremedicated patients only blood gas determinations were done before and after nitroglycerin to evaluate a possible combined effect of nitroglycerin and morphine-scopolamine premedication on blood gases A No 20 gauge plastic cannula was inserted into the right radial artery for blood sampling and for monitoring arterial blood pressures In both groups pH pCO_2 and PO were measured with an Instrumentation Laboratory analyzer No 213 In Group I a No 7 Swan Ganz thermodilution catheter was inserted percutaneously under local anesthesia into the pulmonary artery via the right internal jugular vein for measurement of pulmonary artery pressure pulmonary arterial wedge pressure central venous pressure and cardiac output All pressures were monitored continuously with No 500 Sanborn transducers and recorded on a multichannel recorder (Brush Mark 220) ECG Lead II was also recorded Cardiac output was determined by thermodilution with an Edwards CAB Model 4510 A cardiac output computer In both groups studies were performed before the induction of anesthesia

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Received for publication Sept 12 1977

Accepted for publication Nov 18 1977

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with the patient in the supine position breathing room air Arterial blood gases and hemodynamic parameters were determined before and 10 minutes after the taking of sublingual nitroglycerin 0 6 mg dissolved in 0 5 ml saline Student s t values were used for statistical analysis

Results

PaO_2 fell after nitroglycerin in all but one of the 21 patients studied In the 13 premedicated patients (Group I Table I) PaO decreased from a mean of 65 S D ± 13 to 55 S D ± 11 (p < 0 001) following the administration of nitroglycerin pH and pCO did not change significantly

After nitroglycerin (Table II) mean arterial pressure decreased from a control value of 91 S D ± 8 to 74 S D ± 3 mm Hg (p < 0 001) central venous pressure fell from 5 9 S D ± 2 6 to 2 6 S D ± 2 6 mm Hg (p < 0 001) pulmonary artery pressure fell from 16 S D ± 4 to 10 S D ± 4 mm Hg (p < 0 001) pulmonary arterial wedge pressure dropped from 8 6 S D ± 3 2 to 3 3 S D ± 2 5 mm Hg (p < 0 001) cardiac index decreased from 2 68 S D ± 0 5 to 2 31 S D ± 0 4 L /min /M (p < 0 001) the calculated values for systemic and pulmonary vascular resistance were not significantly altered and heart rate was not significantly changed In the eight unpremedicated patients (Table III) PaO also fell after nitroglycerin from a mean value of 78 S D ± 10 to 64 S D ± 8 mm Hg (p < 0 001) pH and pCO_2 did not change significantly Initial PaO values were higher in the unpremedicated group 78 S D ± 10 vs 65 S D ± 13 mm Hg in the premedicated patients This difference was significant (p < 05) The fall in PaO after nitroglycerin was also slightly greater in the unpremedicated group 14 S D ± 5 vs 10 S D ± 8 mm Hg in the premedicated group This difference however was not statistically significant From this small sampling it would appear that morphine–scopolamine premedication lowered initial PaO values but had no effect on the magnitude of the change in PaO after nitroglycerin

Discussion

This study gives conclusive evidence that sublingual nitroglycerin adversely affects arterial PaO_2 levels in most patients with coronary artery disease breathing room air The cause however remains obscure Arterial PCO_2 did not change after nitroglycerin thus alveolar ventilation was not decreased Nitroglycerin is reported[1] to relax bronchial musculature so an increase in the unevenness of ventilation is unlikely As mentioned previously morphine-scopolamine premedication appeared to lower initial PaO_2 values but the fall in PaO_2 after nitroglycerin was about the same with or without premedication The reduction of PaO_2 after nitroglycerin then would seem to be related to hemodynamic changes that occur after its administration Several possibilities exist (1) vasodilation in poorly or non ventilated areas of the lungs (2) opening of arteriovenous anastomoses which bypass alveoli (the fact that calculated pulmonary vascular resistance did not change after nitroglycerin does not rule out these two possibilities because calculated pulmonary vascular resistance may remain unchanged even though pulmonary vasomotor tone has been altered considerably)[2] (3) the fall in pulmonary artery pressure might favor perfusion to dependent less well ventilated regions of the lungs (4)

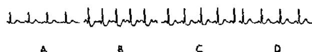


Fig 1 E C G of a patient *A* Before angina pectoris *B* after onset of chest pain *C* ten minutes after NTG (0 6 mg) *D* five minutes after breathing 100 per cent oxygen

Table I Premedicated patients

	Control data			*Data 10 minutes after NTG*		
Case No	*pH*	*PCO*	*PO*	*pH*	*PCO*	*PO*
1	7 37	44	59	7 45	39	48
2	7.38	44	88	7 44	40	58
3	7.35	45	69	7 36	45	51
4	7 42	41	59	7 45	34	52
5	7 42	40	66	7 43	35	52
6	7.38	38	62	7 42	32	50
7	7 44	37	55	7 41	40	55
8	7 41	38	55	7 44	35	49
9	7 44	34	55	7 44	32	57
10	7 41	38	52	7 40	38	48
11	7 40	44	87	7 40	47	85
12	7 40	44	87	7 40	47	73
13	7 41	38	50	7 42	38	43
Mean	7 38	40 3	64 9	7 42	38 6	55 1
S D ±	0 07	3 5	13 8	0 02	5 1	11 4

Chang not significant from control val es.
Change significantly different from control v lues (p < 001)

Table II Hemodynamic data before and 10 minutes after nitroglycerin

	Control data								Data 10 minutes after NTG							
Case No	*HR*†	*MAP*	*CVP*	*PA*	*PAW*	*CI*	*SVR*	*PVR*	*HR**	*MAP***	*CVP***	*PA**	*PAW*	*CI**	*SVR*	*PVR*
1	72	103	5	18	12	2 59	1504	93	75	70	1	10	5	2 13	1 04	94
2	60	89	4	14	6	3 27	1066	100	63	80	0	6	1	2 68	[illegible]	[illegible]
3	58	90	4	14	5	2 76	1081	138	65	70	0	9	1	2 62	9[illegible]8	106
4	75	98	6	15	10	2 85	1226	54	80	80	1	6	3	2 51	1194	46
5	58	94	6	12	7	1 85	1660	94	60	81	1	6	2	1 79	1564	8
6	72	102	4	16	8	3 04	1354	221	78	72	2	12	3	2 67	1100	141
7	69	91	6	16	8	2 36	1510	142	60	76	4	11	2	1.91	1641	[illegible]00
8	68	78	6	16	8	1 87	1264	171	60	88	4	11	2	1 12	1500	[illegible]05
9	68	92	2	12	6	2 02	1935	143	68	90	0	10	2	1 80	216[illegible]	1[illegible]
10	86	83	9	19	9	2 28	1617	218	88	78	8	16	6	1 55	22[illegible]8	322
11	68	100	10	21	11	2 64	1555	172	70	83	4	9	5	2 67	1389	0
12	65	75	4	10	6	2 92	1054	98 2	68	76	2	6	2	2 56	101[illegible]	13[illegible]
13	74	88	11	26	17	3 94	1635	177	55	88	7	21	10	3 03	1134	145
Mean	68 6	91	5 9	16	8 6	2 68	1419	138	68 4	74 3	2 6	10 2	3 3	2 31	1457	13[illegible]
SD ±	7 6	8 6	2 4	4 2	3 2	0 58	260	51 6	9 5	6 2	2 6	4.3	2 5	0 6[illegible]	416	59 9

= Change not significant from control values
= Change significantly different from control values ($p < 001$)
†HR = heart rate (beats/min) MAP = mean arterial pressure in mm Hg CVP = central venous pressure PA = mean pulmonary artery pressure PAW = pulmonary arterial wedge pressure CI = cardiac index SVR = systemic vascular resistance PVR = pulmonary vascular resistance (dynes sec cm)

Table III Unpremedicated patients

	Control data			Data 10 minutes after nitroglycerin		
Case No	*pH*	*PCO*	*PO*	*pH*	PCO_2*	PO_2*
1	7 44	36	90	7 40	44 5	69
2	7 40	42 5	80	7 40	41	64
3	7 40	30	91	7 40	31	70
4	7 43	34	77	7 45	35	67
5	7 39	39	70	7 44	36	64
6	7 45	30	86	7 42	35	74
7	7 48	37 1	69	7 46	35 5	58
8	7 43	35	62	7 44	36	49
Mean	7 43	35 4	78 1	7 43	37	64
S D ±	0 3	4 3	10	02	4 1	8 0

Change not significant from control values
Change significantly different from control values ($p < 001$)

several theoretical studies[3,5] suggest that the observed decrease in cardiac output could account for the fall in PaO_2 However, to the best of our knowledge there is no experimental evidence to support these theories Further studies will obviously be necessary

Several clinical implications can be derived from these findings

1 A fall in PaO_2 could conceivably explain inadequate pain relief experienced by some patients after taking nitroglycerin, i e despite the decrease in wall tension produced by nitroglycerin, myocardial hypoxia may still result from a decrease in available oxygen A trial with high inspired oxygen concentrations along with nitroglycerin would seem indicated in such patients Pertinent to this two patients experienced anginal pain before induction of anesthesia that was still present 10 minutes after 0 6 mgm sublingual nitroglycerin One hundred per cent oxygen was then started and complete relief occurred within five minutes ST segment depression occurred in one of these patients and remained so after nitroglycerin but returned to base line after five minutes of 100 per cent oxygen (Fig 1) Although this strongly suggests that 100 per cent oxygen was helpful to these patients it is also possible that spontaneous resolution of the process could have occurred during the time oxygen was being administered

2 This study lends support to the use of high inspired oxygen concentrations when narcotics and nitroglycerin are used in combination for the treatment of anginal pain

3 When preoperative narcotic medications are given to patients with severe coronary artery

disease some form of oxygen therapy should probably be started shortly after their administration

4 Rarely patients with coronary artery disease appear to have a paradoxical response to nitroglycerin i e the nitrate causes ST segment changes and an increase in anginal pain It has been postulated but not demonstrated angiographically that the vasodilators may further diminish blood flow to ischemic myocardium (coronary steal syndrome)[6] In attempting to define the mechanisms of myocardial ischemia attributed to coronary steal syndrome we suggest that a decreased availability of oxygen initiated by nitroglycerin should also be considered It would be of interest to measure PaO_2 before and after nitroglycerin in these patients and to see if 100 per cent oxygen is beneficial

Summary

The effect of nitroglycerin on arterial blood gases and cardiovascular hemodynamics were studied in patients with coronary artery disease

In 13 premedicated patients blood gases and cardiovascular hemodynamics were studied before and 10 minutes after sublingual nitroglycerin (0 6 mg) In eight unpremedicated patients only blood gases were determined before and 10 minutes after sublingual nitroglycerin 0 6 mg All studies were performed before induction of anesthesia with the patients in the supine position breathing room air

In both groups arterial PO_2 decreased significantly ($p < 0\ 001$) pH and pCO_2 did not change In the 13 patients on which hemodynamic studies were performed the mean arterial pressure ($p < 0\ 001$) cardiac index ($p < 0\ 001$) central venous pressure ($p < 0\ 001$) pulmonary artery ($p < 0\ 001$) and pulmonary artery wedge pressure ($p < 0\ 001$) decreased Calculated values for systemic and pulmonary vascular resistance were not significantly altered ($p > 0\ 4$) This study gives conclusive evidence that nitroglycerin reduces arterial PO_2 in most patients with coronary artery disease breathing room air in the supine position The possible mechanisms and clinical implications are discussed

We thank Miss Dorothy Hollander for technical assistance and Mrs Mary Rogers for preparation of the manuscript

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Table II Hemodynamic data before and 10 minutes after nitroglycerin

Case No	*Control data* HR†	MAP	CVP	PA	PAW	CI	SVR	PVR	*Data 10 minutes after NTG* HR*	MAP	CVP *	PA *	PAW	CI**	SVR	PVR
1	72	103	5	18	12	2 59	1504	93	75	70	1	10	5	2 13	[illegible]	[illegible]
2	60	89	4	14	6	3 27	1066	100	63	80	0	6	1	2 88	[illegible]	[illegible]
3	58	90	4	14	5	2 76	1081	138	65	70	0	9	1	[illegible]	[illegible]	106
4	75	98	6	15	10	2 85	1226	54	80	80	1	6	3	2.51	1194	[illegible]
5	58	94	6	12	7	1 85	1660	94	60	81	1	6	2	1 79	1564	8
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7	69	91	6	16	8	2 36	1510	142	60	76	4	11	2	1.91	1641	[illegible]
8	68	78	6	16	8	1 87	1264	171	60	88	4	11	2	[illegible]	1500	[illegible]
9	68	92	2	12	6	2 02	1935	143	68	90	0	10	2	1 80	[illegible]	[illegible]
10	86	83	9	19	9	2 28	1617	218	88	78	8	16	6	1 55	[illegible]	[illegible]
11	68	100	10	21	11	2 64	1555	172	70	83	4	9	5	[illegible]	1389	0
12	65	75	4	10	6	2 92	1054	98 2	68	76	2	6	2	2 56	[illegible]	[illegible]
13	74	88	11	26	17	3 94	1635	177	55	88	7	21	10	3 03	1134	145
Mean	68 6	91	5 9	16	8 6	2 68	1419	138	68 4	74 3	2 6	10 2	3 3	2 31	[illegible]	[illegible]
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= Change not significant from control values
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†HR = heart rate (beats/min) MAP = mean arterial pressure in mm Hg CVP = central venous pressure PA = mean pulmonary artery pressure PAW = pulmonary arterial wedge pressure CI = cardiac index SVR = systemic vascular resistance PVR = pulmonary vascular resistance (dynes sec cm)

Table III Unpremedicated patients

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2	7 40	42 5	80	7 40	41	64
3	7 40	30	91	7 40	31	70
4	7 43	34	77	7 45	35	67
5	7 39	39	70	7 44	36	64
6	7 45	30	86	7 42	35	74
7	7 48	37 1	69	7 46	35 5	58
8	7 43	35	62	7 44	36	49
Mean	7 43	35 4	78 1	7 43	37	64
SD ±	0 3	4 3	10	02	4 1	8 0

Change not significant from control values
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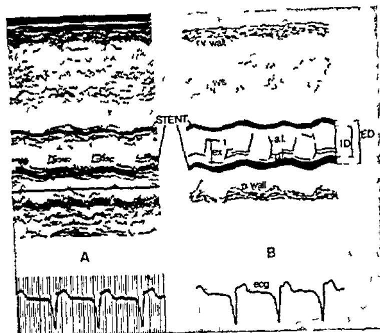


Fig 1 Echocardiogram *(A)* and line drawing *(B)* showing a porcine heterograft valve in the mitral position Note the faint echoes from the valve leaflets within the heavier stent echoes *ED* = external stent diameter *ID* = internal stent diameter *EX* = total leaflet excursion *AL* = anterior leaflet *PL* = posterior leaflet *RV wall* = right ventricular wall *IVS* = echoes from the area of the interventricular septum *P wall* = posterior left ventricular wall.

fourth intercostal space at the left sternal border superiomedial angulation recorded the left atrium and the aorta and the porcine heterograft valve stent and leaflets in the aortic position The inferolateral angulation normally used to record the mitral valve produced echoes from the porcine heterograft stent and leaflets in the mitral position with the interventricular septum anteriorly and posterior left ventricular wall or left atrium posterior to the prosthetic valve High gain and low reject settings were often needed to bring out the faint echoes of the valve leaflets In some cases placement of the transducer farther from the left sternal border was helpful in recording leaflet echoes

Measurements for porcine heterograft valve in mitral position The external stent diameter (ED) was measured as the distance between the outer echoes of the anterior and posterior stent (Fig. 1) The internal stent diameter (ID) was measured from the posterior echoes of the anterior stent to the anterior echoes of the posterior stent These diameters were recorded at their maximum value The ratio of the internal to external stent diameter was then calculated The D E excursion of the anterior leaflet was measured in all cases In cases where a posterior leaflet could be recorded the posterior leaflet excursion and total leaflet opening were measured

The initial posterior diastolic slope of the anterior valve stent was measured in all cases (Fig 2) The diastolic (EF) slope of the valve leaflets was in most cases identical to that of the stent (Fig 1) but occasionally was faster (Fig 2) and was recorded in all cases When the EF slope varied due to atrial fibrillation or due to transducer angle the fastest slope was measured The left ventricular outflow tract was measured at end systole just prior to posterior motion of the valve stent

Measurements of the heterograft in the aortic position The external and internal stent diameters were measured and the ratio was determined in the same manner as heterografts in the mitral position (Fig 3) The maximal excursion of the anterior and posterior leaflets was measured in all patients

Results

Heterograft valves in the mitral position Auscultatory findings did not correlate with postoperative class time post surgery or valve

Echocardiographic evaluation of porcine heterograft valves in the mitral and aortic positions

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Porcine aortic valves, mounted on a flexible stent[1] and preserved with gluteraldehyde, are being used in increasing numbers for valve replacement in both the mitral and aortic position, with good results over a follow up period that now extends to seven years [9] The low incidence of emboli even without anticoagulation, has been the major advantage over conventional replacements However prosthetic stenosis due to thrombus formation has been reported,[3, 10] and significant gradients have been found at postoperative catheterization [7, 8] A small percentage of earlier models of the porcine heterograft valves have shown tissue degeneration with cusp perforation [4] and early, though minor pathologic changes have been seen in the presently available device [10] For this reason, non invasive assessment of this prosthesis is important and echocardiographic studies of 31 patients have previously been described [11, 1] all with valves in the mitral position No correlative catheterization and echocardiographic study is available We have studied the echocardiograms in 15 additional patients as well as in seven patients with valves in the aortic position and present our results combined with those previously reported, in an attempt to provide criteria for the range of movement of normally functioning valves In addition postoperative catheterization studies in three of these patients are presented and their implications are discussed

Materials and methods

Of 36 patients who underwent valve replacement with porcine heterograft valves at the Vanderbilt University Hospital or Nashville Veterans Administration Hospital from Jan 29 1975 to Jan 28 1976 21 were available for echocardiographic study and clinical examination one to 19 months after surgery and comprise the study population Additional patients were contacted by telephone to determine if our study population was similar to the total group Fifteen patients had mitral valve replacement and seven had aortic valve replacement one having both. The average age of patients with mitral replacement was 45 years (range 19 to 67 years) and the patients with aortic valve replacement had an average age of 43 years (range 19 to 67 years) Clinical data are presented in Tables I and II These patients are not representative of the total operated group because of three in whom the clinical status prompted re catheterization However those not catheterized were representative of the total group as far as could be determined by telephone conversation with the patients and their physicians Clinical data on the entire group are available on request

Echocardiograms were performed with an Ekoline 20 ultrasonoscope using a 2 25 mega Hertz 13 mm nonfocused transducer with a repetition rate of 1 000 cycles per second Recordings were made on a Cambridge strip chart recorder With the transducer in the third or

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Received for publication Sept. 20 1977
Accepted for publication Nov 9 1977

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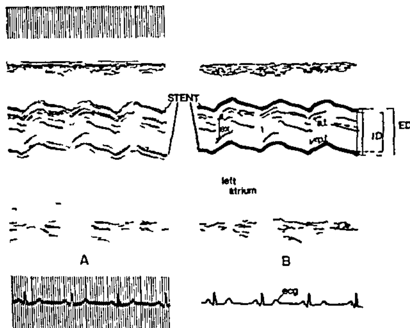


Fig 3 Echocardiogram *(A)* and line drawing *(B)* of a porcine heterograft valve in the aortic position Note the excess echoes within the valve stent emanating from the muscular leaflet of the heterograft and giving the appearance of valve deformity Abbreviations as in *Figs 1 and 2*

Table I Patients with mitral valve replacement

Pt	*Age Sex*	*Length of follow up (months)*	*Diagnosis*	*Status preop*†	*Status postop*†	*Anti coagulation*	*Comments*
J L.	56F	19	MS‡	III	II		
A P	52M	11	MS	III	I	+	1 month after study died of paratracheal bleed secondary to over anticoagulation
C W	41M	12	MR 2 paravalvular leak	IV	II		Bjork Shiley mitral valve replaced for mitral regurgitation
R D	32M	16	MR/AR	IV	II		Both aortic valve and mitral valve replaced with porcine valves
E C	57F	12	MS/AS	IV	II	+	Bjork Shiley put in aortic position
C.J	49M	5	MS/MR/AS	IV	I	+	Bjork-Shiley put in aortic position
N G	27F	13	Wada mitral valve	II	II		Wada valve replaced prophylactically
C R	65M	1	MS	IV	II	+	S/P aortic valve replacement with Starr Edwards valve
P D	6?M	12	MR 2 IHD	IV	II		
R B	19F	7	MR	III	I		
I H	50F	5	MS	III	I	+	Left atrial thrombus at operation
K G	45M	9	MR	IV	II	+	S/P ASD repair persistent atrial arrhythmias
M L.	45F	13	MR 2 IHD	IV	I		Coronary artery bypass to LAD and RCA
J L.	3?M	14	MR	III	I	+	Starr Edwards mitral valve replaced because of mitral regurgitation
R.R	45M	3	MR	III	I		Ruptured chordae

* = patients undergoing postoperative catheterization
† = by NYHA Classification
‡Abbreviations MR = mitral regurgitation MS = mitral stenosis AR = aortic regurgitation AS = aortic stenosis IHD = ischemic heart disease
AVR = aortic valve replacement MVR = mitral valve replacement ASD = atrial septal defect

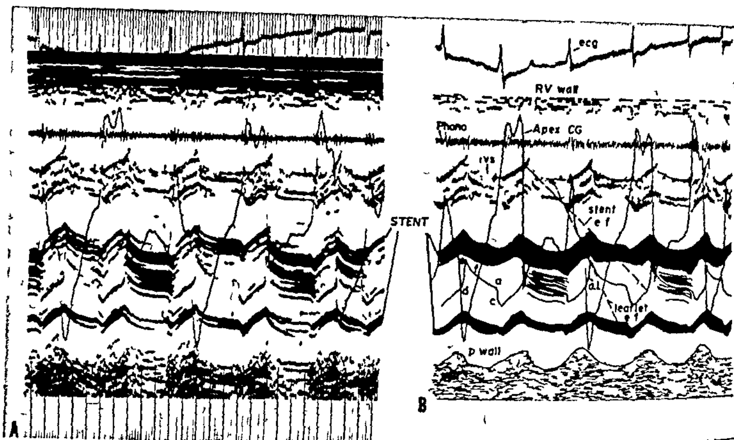


Fig 2 Echocardiogram *(A)* and drawing with labels *(B)* of a porcine heterograft valve in the mitral position Note excessive echoes in vicinity of valve leaflets in second and fourth cardiac cycles *Phono* = phonocardiogram *ECG* = electrocardiogram *RV wall* = right ventricular wall *Apex CG* = apexcardiogram *IVS* = interventricular septum *AL* = anterior leaflet

size A diastolic rumble was frequently heard, occasionally after a soft opening sound Strong echoes from the valve stents were easily recorded in all patients The anterior and posterior stent move in parallel with anterior movement during systole and posterior movement during diastole The external stent diameter agreed with the known valve size within 2 mm in all patients As shown in Figs 1 and 2 the weaker echoes of the valve leaflets are seen between the stent echoes There is abrupt opening of the leaflets at the beginning of diastole with a very rapid opening slope (*D E* Fig 2) The valve leaflets (*leaflet E F* Fig 2) and stent (*stent E F* Fig 2) move posteriorly early in diastole as does the native mitral valve, with the leaflets usually remaining open throughout diastole and closing abruptly at the onset of systole (*A C*, Fig 2) The diastolic posterior movement (E F slope) of the anterior valve leaflet is parallel to the stent movement (Fig 1) and is within the range of E F slopes seen in mitral stenosis Leaflet opening is asymmetrical with the anterior leaflet having a greater excursion This is consistent with the surgical practice of placing the valve so that the larger leaflet is parallel to the interventricular septum Anterior leaflet opening was recorded in all patients but the posterior leaflet could be recorded in only 12 of 15 patients Total leaflet opening could thus be measured only in these 12 An 'a' wave or the fluttering motion seen in native valves in the presence of atrial flutter or fibrillation was inconsistently seen *(See last complex in Fig 1)* Excessive echoes from the vicinity of the valve leaflets were often recorded with higher gain settings and varying transducer position *(compare second and third complexes in Fig 2)* Paradoxical septal motion was noted in six of 16 patients recorded below the mitral valve prosthesis Table III details these results and compares them with those in the literature

Heterograft valves in aortic position Measured external stent diameter, (*ED* Fig 3) agreed within 2 mm to the manufacturer's valve size Internal stent diameter (*ID* Fig 3) averaged 19 8 mm and the mean calculated ratio of internal to external stent diameter was 0 75 with a range of 0 71 to 0 80 The valve leaflets open abruptly in systole, remain open during systole with a gradual anterior movement in parallel with the

able IV Echocardiographic measurements of porcine heterograft valves in the aortic position

Patient	Valve Size	Stent diameter by echo (mm)			Septal motion	Leaflet excursion (mm)		
		External	Internal	Int/Ext		Anterior	Posterior	Total
J F	25	27	20	0 74	N	9	9	18
I D	25	25	20	0 80	N	8	8	16
J J	27	?6	20	0 77	N	8	6	14
R B	2?	27	20	0 74	P	8	9	17
B T	?7	?8	0	0 71	P	8	8	16
A S	27	27	19	0 76	P	10	8	16
Mean of normals			19 8	0 75		8 2	8	16
Range	25 2?	25 28		0 71-0 80		8-10	6-9	14 18
R D	23	23	16	0 ?0	N	?	7	14

= patient evaluated by postoperat ve catheteri ation
Abbreviations Int/Ext = ratio of internal di meter to ext rnal diameter N = n rmal septal motion P = p radoxical septal motion.

alve stent and abruptly close at the end of ystole Anterior and posterior leaflet (*AL* and *PL* Fig 3) opening was usually symmetrical and n some patients a central nonmoving leaflet was recorded In those patients in whom valve opening was asymmetrical either the anterior or posterior leaflet might open to a greater degree consistent with the surgical practice of varying alignment of the prosthesis The total valve excursion (*EX* Fig 3) averaged 16 mm with a range of 14 to 18 mm slightly less than normal native aortic valve opening Excess echoes were seen within the stent in all patients but were variably placed anteriorly or posteriorly Values for individual patients and the mean values and range for the group are shown in Table IV

Hemodynamic correlation Three patients underwent postoperative cardiac catheterization and the results are presented in Table V

Patient N G presented in 1970 with severe mitral regurgitation and heart failure she underwent mitral valve replacement with a Wada prosthesis and improved to Class I status Because of reports of occluder embolization with the Wada valve it was elected to prophylactically replace this with a porcine heterograft because of her excellent clinical status no preoperative catheterization was performed After surgery she developed dyspnea on moderate exertion and fatigue and was catheterized twelve months after surgery one month prior to her echocardiographic study Her cardiac index was depressed at 2 4 and there was mild to moderate prosthetic stenosis with a left atrial-left ventricular diastolic gradient of 8 and a calculated valve area of 1 4 square centimeters The gradient rose to 15 with exercise with no rise in the LVEDP Echocardiographically her valve measurements were all within the previously and presently reported range of normal she did however have the slowest stent and anterior leaflet slope that we have seen although no slower than one clinically normal patient seen by Bloch and colleagues [12]

Patient C W had mitral valve replacement in 1972 for mixed mitral disease but tissue over growth caused prosthetic stenosis and he had a second mitral valve replacement in 1973 Although he was improved for several years increasing congestive failure developed in 197? and a paravalvular leak with severe mitral regurgitation was found After porcine valve replacement he continued to have dyspnea on strenuous exertion Restudy showed only mild prosthetic stenosis The mean gradient was 9 the end diastolic gradient was only 3 the valve area 1 8 square centimeters and the cardiac index is slightly depressed at 2 6 but doubling with moderate exercise On echocardiographic study all parameters were well within the range of normal Pulmonary function tests showed a moderately severe restrictive defect and his symptoms were thought to be primarily due to pulmonary disease

Patient R D had both mitral and aortic valves replaced for severe aortic regurgitation with co existing mitral regurgitation thought due to massive left ventricular dilatation He did very well postoperatively with dyspnea only on extreme exertion but because of a loud persistent systolic murmur was recatheterized His

Table II Patients with aortic valve replacement

Pt	Age Sex	Length of follow up (Months)	Diagnosis	Status preop†	Status postop†	Anti coagu lation	Comments
RD*	32M	19	AR/MR†	IV	II	°	MVR as well with porcine valve
JJ	40M	15	AR	III	I		
JF	25F	11	AR	III	I	°	
RB	53M	11	AR	II	I	°	
PD	19M	2	Bjork Shiley AV with AR	IV	I	°	
BT	66M	9	AR	IV	I	°	
AS	67F	17	AS	II	I	°	

* = patients undergoing postoperation catheterizations
†Abbreviations AR = aortic regurgitation MR = mitral regurgitation MVR = mitral valve replacement AS = aortic stenosis.

Table III Echocardiographic measurements of porcine heterograft valves in the mitral position Present study and review of the literature

Patient	Valve size (mm)	Stent diameter by echo (mm)			Septal motion	LVOT (cm)	Diastolic slope (mm/sec)		Leaflet excursion (mm)		
		External	Internal	Int/Ext†			Stent	Anterior leaflet	Anterior	Posterior	Total
J I	27	28	21	0 75	N	1 5	24	46	11	8	19
A P	27	26	17	0 65	N	2 0	24	24	13	2	15
C W*	27	28	19	0 68	N	1 2	39	39	10	2	1?
R D*	27	25	17	0 68	N	0 9	40	40	8	—	—
E C	29	28	17	0 61	P	1 8	13	13	11	4	15
C J	29	27	17	0 63	P	2 5	20	20	10	—	—
N G*	29	29	18	0 62	N	0 8	11	11	12	4	16
C R	29	28	18	0 64	N	2 0	22	22	10	—	—
P D	31	31	20	0 65	N	2.3	24	32	10	5	15
R B	31	29	19	0 66	N	1 2	20	20	11	4	15
I H	31	30	18	0 60	P	0 7	23	23	12	3	15
K G	31	32	24	0 75	P	1 0	20	30	12	4	16
M L	31	30	17	0 57	P	2 1	24	44	13	3	16
J L	33	33	22	0 67	P	1 2	20	27	14	2	16
R R	33	32	20	0 73	N	1 6	25	25	9	4	13
Mean of present study (range) No of pts = 15	(27 33)	(25 33)	19 (17 24)	0 66 (0 57 0 75)		1 5 (0 7 2 5)	23 3 (11-40)	27 9 (11-46)	11 (8 14)	4 (2-8)	15 (1? 19)
Horowitz et al. No of pts = 20	(27 35)	(28 36)	20 (17 24)	0 66 (0 56-0 74)	P = 7 N = 3 A = 6 T = 4	1 2 (0 5 2 2)	24 (19 33)				15 (10-?1)
Bloch et al No of pts = 10	(27 31)	(19 30)	20 (16 24)	0 77 (0 60 0 84)			21 5 (11-59)	19 (9 38) N = 9			11 (10-14) N = 6
Bloch 1 pt with thrombus	36	indefinite	21				26				
Mean of normals (range)	(27 33)	(19-36)	20 (17 24)	69 (0 50 0 84)		1 4 (0 5 2 5)	23 4 (11 59)	24 5 (9-46)			14 5 (10-?1)

patients evaluated by postoperative catheterization
†Abbreviations Int/Ext = ratio of internal diameter to external diameter N = normal septal motion P = paradoxical septal motion A = abnormal septal motion T = technically inadequate LVOT = left ventricular outflow tract at end-systole

ith tissue mitral prostheses has not been found to correlate with calculated valve areas or diastolic gradients and we concur in this finding An opening sound is also heard in some of these patients again seemingly without hemodynamic significance

Reports of structural changes even in clinically satisfactory valves with inflammatory cells lining the leaflets fibrin thrombus giant cell invasion with focal disruption of collagen and calcium deposition as well as sporadic cases of thrombus causing prosthetic stenosis[5] make noninvasive evaluation of these valves desirable Also postoperative hemodynamic evaluation has shown mitral valve gradients ranging from 0 to 32 mm Hg with calculated valve areas from 0 64 to 3 4 cm² and mean aortic valve gradients from 0 to 83 mm Hg with valve areas from 0 49 to 1 9 square centimeters However these cases have not been evaluated non invasively

Echocardiography has proven useful in the diagnosis of some instances of mechanical prosthetic valve dysfunction but has generally been considered only an adjunct to auscultation and phonocardiography in detecting ball variance or thrombus formation However since ausculatory phenomena have been less helpful with the tissue valves echocardiographic visualization of the valve leaflets themselves might have a more important role especially if it can detect early stiffening or calcification If those hemodynamic factors that alter native valve motion affect prosthetic tissue leaflets in the same manner function as well as anatomy could be evaluated Demonstrated abnormalities in fascia lata prostheses homografts and in one porcine heterograft support the role of echocardiography However only small series of normally functioning heterografts evaluated by echocardiography have been reported making it difficult to be certain if a particular valve s motion is normal The present series confirms the studies of normal values by Bloch and associates[2] and Horowitz and colleagues adding sufficient numbers to present a meaningful range of normal values for stent and leaflet motion in the mitral prosthesis and preliminary data for valves in the aortic position We have also added three cases in which catheterization data can be compared to echocardiographic parameters

Heterograft prostheses in the mitral position

It is not difficult to record echoes from the stent of the heterograft prostheses The external diameter of the ring is quite accurately estimated despite the potential for being misled by reverberations from this echodense structure The ratio of internal to external diameter has been suggested as a guide to detecting thrombosis or fibrosis compromising the valve orifice and our values for this agree with those of other investigators However the internal diameter per se a more direct estimate of orifice size varies considerably and does not correspond well to valve size as can be seen from the wide range of measurements we and others have found This suggests that this value and the ratio may be of use only if a change from a previous study is demonstrated

We found that an anterior valve leaflet could be visualized in all patients although multiple attempts were required in several patients early in the study With practice the last patients could be echoed in no more time than required for a usual clinical echocardiogram We would agree with Bloch and associates[2] that a valve whose anterior leaflet cannot be recorded should be suspected of dysfunction if other cardiac structures can be recorded clearly However an anterior leaflet that can be recorded does not exclude moderate obstruction to flow as our correlations with catheterization data revealed Also as the porcine aortic valve has some muscular tissue in one of its leaflets the presence of excess echoes in the mitral valve area are less suggestive of a thickened valve or valvular vegetations than they would be in the native valve (see Fig 2)

Prosthetic leaflet excursion is less than that of the native mitral valve since the leaflets are shorter Usually the total leaflet excursion falls within the range of normal aortic valve opening with conditions of low flow *in vitro* sequential and incomplete valve opening may be seen[11] and this may contribute to the decreased excursion in some If discrete leaflets are seen values for total excursion that fall below the range presented here suggest a diminished cardiac output As the D E and A C slopes of native valves may vary with alterations in left ventricular diastolic pressures these were of interest but we found them difficult to measure reproducibly because of the short excursion and excess echoes between the stents

The E F slope was not difficult to determine since this slope is slowed in rheumatic mitral

Table V Postoperative hemodynamic data in three patients with porcine heterograft valves

Patient	Time of cath	Catheterization data				CO/CI	MG (mean)	AG (mean & peak)	MVA (cm²)	AVA (cm.)	Comments
		PA†	LA or PCW	LV	Ao						
N G	1970	Left ventricular angiography only showing severe mitral regurgitation in critically ill patient									
	12 mos post op	42/18	v = 22 mean = 16	150/0 12	150/95	3 7/2 4	8	0	1 4		Wada mitral valve replacement in 197. Class I pre op in 19 5, had elective valve replacement and not recatheterized
C W	pre op	60/22	v = 50 mean = 30	90/0 12	90/50	1 9/1 0	16		≥ 5		Severe mitral regurgitation
	8 mos post op	33/12	a = 15 mean = 13 v = 17 mean = 30	125/0 10	125/70	4 9/2 6	9		1 8		No mitral regurgitation. Cardiac output rose to 8 4 l /min with exercise
R D	pre op	85/48	v = 36 mean = 15	170/0 28	120/67	2 2/1 2	0	$\overline{25}$ 52		0 35	Severe aortic regurgitation and moderate mitral regurgitation
	9 mos post op	33/14	v = 17 mean = 10	145/0 10	95/70	7 2/3 9	0	$\overline{42}$ 50		1 2	No mitral or aortic regurgitation

All pressures are expressed in mm Hg
†Abbreviations PA = pulmonary artery LA or PCW = left atrium or pulmonary capillary wedge LV = left ventricle Ao = aorta CO/CI = cardiac output/cardiac index MG = mitral gradient AG = aortic gradient MVA = mitral valve area AVA = aortic valve area

mitral prosthesis was functioning well, with no diastolic gradient but the aortic valve a size 23 (the smallest in this series), had a gradient and reduced valve area The cardiac output and index were normal despite this The aortic valve leaflets opened rapidly by echocardiographic study but were at the low end of the range of our normal valves This valve had the smallest internal diameter and internal to external diameter ratio we have seen His mitral prosthesis had a diastolic slope in the normal range but the lowest anterior leaflet excursion

Due to the small number of patients no definite conclusions can be reached but the data suggest a relationship between the calculated mitral valve area and the diastolic slope of the stent Diastolic E F slopes were faster in the two patients with either no gradient or a large valve area and slowest in the patient with the smallest valve area None of these patients was sufficiently symptomatic to require re operation so we have no pathological data regarding the status of their valves

Discussion

Porcine heterograft valves have several advantages over mechanical prosthetic valves The reported rate of thromboembolism without anticoagulation over long term follow up of 6 to years has generally ranged from 0 2 0 per cent per patient year, with most emboli occurring in the first 3 months usually in patients with atrial fibrillation[6, 7, 9, 13, 16] Most institutions at present anticoagulate only patients with atrial fibrillation and even then for a limited period usually 3 months Significant hemolysis has not been reported No externally audible valve sounds make this prosthesis highly acceptable to patients and physicians but the lack of mechanical opening and closing clicks has made clinical evaluation more difficult

The presence of a diastolic rumble in patients

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stenosis one would expect that the heterograft leaflet also would remain open in diastole if there was obstruction to flow This should be true whether the obstruction resulted from leaflet thickening, fusion and/or calcification, or an orifice compromised by fibrosis or thrombus It has been demonstrated that anterior leaflet motion closely approximates annulus motion in mitral stenosis,[18] and the posterior leaflet in diastole follows the same course Since the prosthetic stent is attached to the annulus, stent motion is equal to annular motion Therefore stenotic heterografts might be more likely to have a leaflet E F slope equal to that of the stent, while non stenotic valves would be expected to have a faster E F slope than that of the stent In one case of surgically documented prosthetic stenosis due to thrombus,[12] the echocardiographic appearance of the valve suggested material within the stent as well as an increased stent excursion, a normal stent E F slope, but no distinguishable anterior leaflet E F slope With only three catheterized patients, we cannot test this hypothesis with certainty but since all three patients had equal leaflet and stent slopes and two of these three had mild or no obstruction the absence of a faster leaflet E F slope does not necessarily denote stenosis We found steeper slopes in two patients with mild or no stenosis than in the single case with moderate obstruction Certainly in native valves the E F slope may be reduced by pathology other than mitral stenosis The most common causes are conditions that alter left ventricular filling characteristics such as wall hypertrophy secondary to hypertension or aortic stenosis Further correlations are needed to determine if decreases in slope will parallel the degree of mitral valve obstruction in the absence of left ventricular abnormalities

Heterograft prostheses in the aortic position Opening sounds were not heard with the prosthesis in the aortic position but most patients had a systolic ejection murmur of variable intensity With persistence recording of the prosthetic stent and both anterior and posterior valve leaflets was possible in all patients This did require 30 to 40 minutes in some patients and this prolonged effort often resulted in only a few measurable complexes

The muscular leaflet produced excess echoes in most patients, if discovered later in a patient's course, these might be mistaken for vegetations or thickened leaflets, especially if a baseline postoperative echo was not available for comparison

The total valve opening falls at the lower end of the normal range for native aortic valves with two patients having valve opening less than the lower limit of normal One of these patients was catheterized and had a significant gradient As with the mitral valve, a diminished cardiac output will open the valve less, and it may be difficult to differentiate valvular obstruction due to stiffening or calcification of the leaflets from a low output state The left ventricular echogram may aid in this differentiation, particularly after the early (six months) postoperative period during which paradoxical septal motion will be seen in most patients In small prostheses, where the obstruction to flow is likely to be at the annular level, demonstration of normally moving leaflets will not establish the absence of a hemodynamically significant gradient as shown in our patient, R D In the larger valves, where obstruction may be due to tissue ingrowth or leaflet dysfunction, echocardiography should be more helpful, especially if sequential studies are obtained

Further correlative catheterization-echocardiographic studies should be performed to clarify the hemodynamics of heterograft valve motion and add to our understanding of echocardiographic patterns of stent and leaflet movement these early studies provide a base for further work and help determine whether baseline and sequential echocardiograms will be of significant assistance in the follow up of patients undergoing valve replacement with porcine heterografts

Summary

We evaluated 15 porcine heterograft valves in the mitral position and seven in the aortic position by echocardiography Combining our quantitative description of valve stent and leaflet motion with 31 previously reported cases we suggest echocardiographic criteria for the range of normal porcine heterograft valve motion in the mitral position Quantitative evaluation of valve leaflet and stent motion for valves in the aortic position is described for the first time Correlative hemodynamic and echocardiographic data are provided for three patients who underwent po

operative catheterization The use of echocardio graphy in following the function of porcine hete rograft valves is discussed

We gratefully acknowledge the technical assistance of Mr Dan Wheeler in recording the echocardiograms and the secretarial assistance of Ms Thelma Barrett and Ms Billie Rich We wish to thank Dr Taylor Wray for critical review of the manuscript and illustrations.

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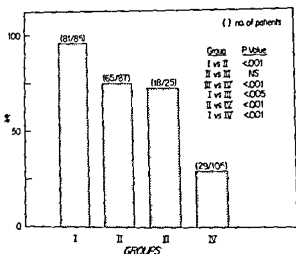


Fig 1 Prevalence of coronary disease (n = 193) in each patient group (n = 302)

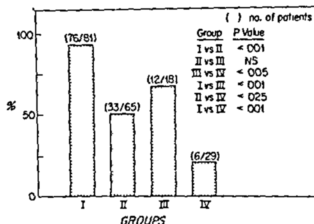


Fig 2 Prevalence of multivessel coronary disease (n = 127) in each patient group with coronary disease (n = 193)

downsloping ST segment depression or elevation was required

The following groups of patients were eliminated from the study Those with valvular heart disease those on digitalis and those whose resting ECG showed LBBB or LVH Patients without exercise induced chest pain or ischemic ECG abnormalities who did not achieve 85 per cent sub-maximal heart rate during exercise were also excluded

Coronary cineangiography was performed in all patients usually the day following the stress test but in no instance were the two studies more than two months apart In each case the decision to do angiography was made prior to the exercise test which was performed as a part of the routine evaluation of these patients The cineangiograms of each major vessel were reviewed in multiple projections For the purposes of analysis coronary artery disease was defined as significant if two or more observers estimated luminal narrowing of a vessel to be greater than 70 per cent

Exercise test sensitivity was defined as the percentage of patients with documented coronary disease having a positive ECG or chest pain response and specificity was defined as the percentage of patients without coronary disease having a negative ECG or chest pain response Predictive value was defined as the percentage of patients with a positive ECG or chest pain response who also had coronary disease

All analyses of data was carried out using the Chi square test

Results

Patient groups—general characteristics The patients were divided into four groups Group I consisted of 85 patients who during exercise testing developed both chest pain and a positive ECG response Group II consisted of 87 patients who had a negative chest pain response but a positive ECG response Group III consisted of 25 patients with a positive chest pain response but a negative ECG response Group IV consisted of 105 patients who were negative for both chest pain and ECG response

Angiographic correlations The prevalence of coronary disease in each group is shown in Fig 1 Coronary disease was present in 81 of 85 patients (95 per cent) in Group I 65 of 87 patients (75 per cent) in Group II 18 of 25 patients (72 per cent) in Group III and 29 of 105 patients (28 per cent) in Group IV Thus chest pain alone (i e Group III) is as good as ECG changes alone (i e Group II) in predicting the presence of coronary disease Moreover the concordance of chest pain and ECG response either positive as in Group I or negative as in Group IV is more highly predictive of the presence or the absence of coronary disease respectively than either response alone

To test whether our data would correlate with the extent of coronary disease the patient groups were also analyzed according to the prevalence of multivessel disease which was defined as significant luminal narrowing (≥ 70 per cent) in two or more major vessels (Fig 2) Group I was again more highly predictive than either Groups II or III Groups II and III did not differ significantly

The predictive value of anginal chest pain as an indicator of coronary disease during exercise testing*

Am Heart J 1978, 96 (4), 458-462

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Exercise testing is the traditional non invasive method of evaluating patients with chest pain for the presence of coronary artery disease The classical response has been measured in terms of ST segment depression alone Using only that criterion the prevalence of false negative responses varies from 20 to 65 per cent [1]

It is the purpose of this report to present our experience using anginal chest pain induced by exercise as an additional and independent criterion for a positive exercise response The goal was to determine if such chest pain would increase the yield of true positive responses and correlate with the extent of coronary disease To accomplish this objective, exercise test data were reviewed on a group of patients referred for cardiac catheterization who had exercise tests just prior to the catheterization

Methods

The patient population who were studied retrospectively consisted of 302 patients who underwent both an exercise test and coronary angiography at University Hospital in the last four years The patients were studied because of possible or definite ischemic heart disease All patients underwent graded exercise on a bicycle ergometer or treadmill the latter using the Bruce protocol [2] A 12 lead ECG was recorded at rest, at 3 minute intervals during the exercise test and during 10 minutes of recovery All patients were exercised to an end point consisting of fatigue or chest pain repetitive ventricular arrhythmias or greater than 4 mm ST segment depression on the electrocardiogram Patients who developed characteristic anginal chest pain (i e substernal pressure-sensation with or without radiation which increased with continuing exercise) during the exercise test were asked to grade it on a scale from 1 to 4, 1 being mild and 4 being severe The exercise test was stopped if the patient developed either 3+ anginal chest pain alone or 2+ anginal chest pain associated with other clinical evidence of significant ischemia For the purposes of analysis, a positive chest pain response was defined as anginal chest pain of grade 2 or more severity Pain which was judged by the exercise physiologist and the physician supervising the test to be musculoskeletal in origin or related to respiratory efforts or which was atypical in character was considered a negative chest pain response A positive ECG response was defined as the appearance of 1 mm of horizontal or downsloping ST segment depression, or 1 mm of ST segment elevation If the resting ECG had abnormal ST segments an additional 1 mm of horizontal or

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Supported by United States Public Health Service Grants HL 14646 N01 HV 53001 RR 533 and HL-18318

Received for publication Oct 3 1977

Accepted for publication Nov 18 1977

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*Presented in part at the 49th Scientific Sessions of The American Heart Association November 1976.

0002 8703/78/100458 + 05$00 50/0 © 1978 The C V Mosby Co

and 23 per cent and 65 per cent of patients with neither response Thus it appears that exercise induced chest pain not only adds to the predictive value of an ischemic ECG response but also by itself predicts coronary disease as accurately as an ischemic ECG response alone

Conversely the presence of a totally negative response (Group IV) predicted the absence of significant coronary disease in 72 per cent of patients studied We recognize that due to the selection bias of our sample population consisting of patients referred for cardiac catheterization we have probably overestimated the predictive value of chest pain and an ischemic ECG response as they would apply to the general population [13] By the same token we may have underestimated the ability of a doubly negative exercise test to predict the probability of the absence of significant coronary disease

The sensitivity of the exercise test varies with the type of stress test employed and the criterion used for an ischemic ST segment response ranging between 35 and 80 per cent [1] By using computers to measure an ST segment index [1] and by including the criterion of a slowly upsloping ST segment depression [17] it is possible to increase the sensitivity of the stress test although the specificity may concurrently be decreased Our data suggest that the sensitivity of the exercise test could be increased to 85 per cent by including the criterion of exercise induced chest pain with or without ischemic ECG changes at the expense of a slightly decreased specificity (Table I) These results are in agreement with other studies in the literature which considered the chest pain response to exercise [2] (Table I) If the value of exercise induced chest pain response alone is analyzed the specificity is very high (90 per cent) but the sensitivity is much lower (51 per cent)

Certain other clinical signs or ECG changes during an exercise test have recently been shown to predict increasing severity of coronary disease These have included myocardial ischemia occurring early on in the exercise period [6] or extending late into recovery [7] the presence of hypotension during exercise [6] extreme ST segment depression [1] inadequate heart rate response to exercise [20] and serious ventricular arrhythmias [1, 22] during exercise The data presented here indicate that exercise induced chest pain associated with ischemic ECG changes predicts multivessel coronary disease more accurately than either response separately Although an ischemic ECG response alone was more predictive of multivessel coronary disease than a totally negative exercise test which agrees with other studies [8, 23, 24] the combination of chest pain and ischemic ECG response was even more predictive Although Lindsey and Cohn[25] could not find any difference between 74 patients with chest pain and ischemic ECG changes compared to 39 patients with only ischemic ECG changes alone in terms of extent of coronary disease our findings are in agreement with the studies of Jelinek and colleagues[12] and Tonkon and co workers [6] both of whom found that patients with exercise induced ischemic ECG changes and chest pain were more likely to have multivessel disease A recent study by Cole and Ellestad[27] analyzed 950 patients in terms of coronary events and mortality after five years of follow up and found that patients with exercise induced anginal pain plus ischemic ST changes had a worse prognosis than patients with only ischemic ST changes Thus it appears that the concordance of exercise induced anginal chest pain and ischemic ECG changes correlates with the severity of coronary disease by both angiographic and long term follow up studies

Summary

To determine the significance of anginal chest pain during exercise testing a series of 302 patients undergoing coronary arteriography with exercise testing was reviewed Of the 302 patients 85 had ischemic ECG changes and chest pain (Group I) 87 patients had ischemic ECG changes but no chest pain (Group II) 25 patients had chest pain but no ischemic ECG changes (Group III) 105 patients had neither chest pain nor ischemic ECG changes (Group IV) Coronary artery disease was present in 95 per cent of Group I 75 per cent of Group II 72 per cent of Group III and 28 per cent of Group IV Of those patients with coronary disease multiple vessels were involved in 94 per cent of Group I 51 per cent of Group II 67 per cent of Group III and 21 per cent of Group IV The predictive value for presence and extent of coronary disease showed Group I > Groups II and III > Group IV ($p < 0.025$) We conclude that (1) anginal chest pain during exercise testing predicts the presence and extent of coronary disease more accurately than its absence (2) the presence of chest pain even

Table I Comparison of results in seven studies

	Sensitivity			Specificity			Predictive value	
	Positive chest pain alone	Positive ECG alone	Positive ECG and/or chest pain	Positive chest pain alone	Positive ECG alone	Positive ECG and/or chest pain	Positive chest pain	Positive ECG
This study (n = 302)	51%	76%	85%	90%	76%	70%	90%	85%
Keleman et al[7] (n = 74)	85%	54%		100%	96%		100%	96%
Bartel et al (n = 650)	45%	65%	*		92%	*	86%	
Piessens et al. † (n = 40)	70%	65%	83%	90%	83%	77%	90%	84%
Eriksen et al.[1] (n = 105)	25%	84%		83%			74%	69%
Rios and Hurwitz[11] (n = 50)	41%	83%	83%	*	90%	*	*	9[illegible]%
Jelinek et al ‡ (n = 153)	62%	57%	78%	67%	82%	54%	90%	93%

*Results could not be obtained because of insufficient data
†Includes 1 5 mm upsloping ST segment depression as positive ECG criterion
‡Master's test Includes 0 5 mm of horizontal or downsloping ST segment depression as a positive test

from each other, and Groups II and III were more highly predictive than Group IV

Clinical correlations Among the 302 patients, 172 (57 per cent) had an ischemic ECG response on the exercise test and 146 of these patients (81 per cent) had significant coronary disease Of interest is the fact that only 85 of 146 patients (56 per cent) with ischemic ECG changes and documented coronary disease had anginal chest pain precipitated by exercise testing

On the other hand, 110 of 302 patients (36 per cent) developed anginal chest pain during the exercise test and of these 99 (90 per cent) had coronary disease Of these latter 99 patients with exercise induced chest pain and coronary disease 81 (82 per cent) had an ischemic ECG response

Discussion

Classical angina pectoris by history has been found to be highly predictive of coronary disease ranging between 85 and 92 per cent[3,6] However when patients with atypical chest pain were analyzed by subsequent coronary angiography only 29 to 66 per cent were found to have coronary disease[3,6] In our series we found that the predictive value of exercise induced anginal chest pain (independent of ECG changes) was 90 per cent, which was comparable to the 85 per cent predictive value of exercise induced ischemic ECG changes (Table I) Other authors[7,11] have also found that chest pain precipitated by exercise testing correlates to a high degree with the presence of coronary disease ranging from 74 to 100 per cent (Table I) Thus chest pain during the exercise test may be a more reliable method of evaluating a patient's symptoms than the clinical history of chest pain (which may contain many atypical features), and is as good or better in predicting the presence of coronary disease

Our data indicate that exercise induced chest pain combined with ischemic ECG changes predict the presence of coronary disease more reliably than either response alone Both the occurrence of exercise induced chest pain alone and ischemic ECG changes alone were better in predicting coronary disease than the total absence of these responses These results are in agreement with two smaller series reported by Piessens and associates[9] and by Jelinek and colleagues[12] who found that the combination of chest pain and ischemic ECG changes predicted coronary disease in 96 per cent and 98 per cent of their patients, respectively compared to 78 per cent and 86 per cent of patients with just exercise induced chest pain 56 per cent and 80 per cent of patients with just ischemic ECG changes alone

Perioperative myocardial infarction related to coronary bypass surgery

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The incidence of postoperative transmural myocardial infarction after coronary bypass surgery has been reported as ranging from 10 per cent to 35 per cent [6] This study was made to determine the incidence of transmural myocardial infarction within the first 10 days after aortocoronary artery bypass surgery to correlate the serum enzyme values with the diagnosis of transmural myocardial infarction occurring in the early postoperative period to compare graft patency and left ventriculographic findings in groups with and without infarction and to determine the clinical course of patients with perioperative infarction

Materials and methods

Preoperative and serial postoperative electrocardiograms of 1 582 patients who underwent coronary bypass grafting in 1973 were analyzed and stored in an automated cardiovascular information registry Only development of new Q waves was accepted as evidence of acute infarction ST T wave changes regardless of characteristics were not accepted as evidence of infarction in the absence of Q waves The electrocardiograms of the group with postoperative infarction and those without infarction but with serum glutamic oxaloacetic transaminase (SGOT) levels of 100 or more units on any of the first three postoperative days were retrieved and reviewed by two cardiologists If both agreed on the diagnosis the patient was considered to have infarction

In all patients blood was drawn for serial postoperative determinations of SGOT and creatine phosphokinase (CPK) values in the first second and third days after operation Since different methods were used in the determination of the CPK level this enzyme was not used for correlative study

Preoperative coronary arteriography was performed by the Sones and Shirey technique [7] In 45 of the 94 patients with early postoperative transmural myocardial infarction and in 141 consecutive patients in the group without infarction postoperative angiography of the bypass grafts was performed with selected coronary arteriography 1 to 20 months (mean 11 5 months) and 6 to 28 months (mean 15 months) respectively from the date of operation

The left ventriculograms were examined in the right anterior projection for localized areas with diminished or absent contractions Preoperative and postoperative angiograms were compared for possible changes in segmental wall motion The postoperative ventriculograms with new areas of diminished or absent contractions were interpreted as worse and those with disappearance of previously abnormal contraction areas were considered improved

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Received f publi tion Oct. 3 1977

Accepted f publ tio Dec 1 1977

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0002 8703/ 8/1 + 04$00 40 0

without an ischemic ECG response during exercise testing appears to be as predictive of coronary disease as an ischemic ECG response alone, and (3) the combination of anginal chest pain during exercise testing and an ischemic ECG response is highly predictive of multivessel coronary artery disease

The authors would like to acknowledge the secretarial assistance of Ms Marie Gardner

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Improvement in contractility was noted in some patients in the group without infarction but not in the group with infarction

Clinical course in group with infarction Follow up information (Table V) was obtained in all patients with infarction after they were discharged from the hospital The minimum follow up period was 12 months (mean 26 9 months) with two deaths occurring at 2 and 8 months of follow up Almost half the patients continued to have chest pain Post hospital infarction occurred in one patient 4 months after operation Congestive heart failure was noted in four patients followed 36 to 39 months Reoperation was done in two symptomatic patients with graft failure One patient required a permanent pacemaker at 34 months for sick sinus node syndrome and lastly one patient was confined to a long term care institution for dementia

Discussion

The mechanism of transmural myocardial infarction during coronary bypass surgery is unknown Early graft occlusion is probably not the only cause of infarction The incidence of this complication may be related to a combination of factors which may include the selection of the vessels to be grafted cardiopulmonary perfusion time and mean arterial pressure period of anoxic arrest and ventricular fibrillation and bypass graft patency rate In our study there was a significant difference in the status of the bypass graft in the groups with and without transmural infarction ($p < 0.001$) and early graft closure was found in 49 per cent of the infarction However evidence of myocardial infarction is not a reliable indication of graft status supplying the zone of infarction since 51 per cent of these patients had patent grafts Postmortem examination in the small group with postoperative mortality confirmed the occurrence of myocardial infarction in areas supplied by patent grafts Similar observations have been made by others [3]

The accuracy of the serum enzyme in diagnosing transmural myocardial infarction was low with only 49 per cent of patients with SGOT of 100 or more units having myocardial infarction However except for one patient all patients with transmural myocardial infarction had this enzyme level It would appear that perioperative transmural myocardial infarction is unlikely if

Table IV Postoperative angiographic findings in groups with and without infarction

	Group with infarction (45 patients)	Group without infarction† (141 patients)
Patients with at least one graft occluded	22 (49%)‡	24 (17%)
Postoperative left ventriculogram		
Unchanged	17	106
Worse	?8 (62%)	20 (14%)
Improved	0	15

Includes only patients who had postoperative angiography
†First consecutive pati nts who returned for postoperat e angiography
‡Includes only p tients with occlusion of graft to vessel supplying area of infarcti n

Table V Post hospital course of patients with infarction

	No of patients
No chest pain	3?
Pain suggesting angina	40
Subsequent infarction	1
Congestive failure	4
Reoperation	2
Pacemaker implant	1
Dementia	1
Deaths	2
Total	83

the SGOT level in the first three postoperative days is less than 100 units

Intraoperative infarction is associated with an increase in mortality and morbidity The five postoperative hospital deaths in the group with infarction indicate a 5 3 per cent operative mortality rate Two subsequent deaths a few months after surgery and the development of congestive failure in four other patients could well be related to the occurrence of perioperative infarction Because almost half the patients in the infarction group has occluded grafts to vessels supplying areas of infarction graft occlusion and the attendant infarction may be a factor in the less satisfactory symptomatic improvement [14]

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Table I Operative mortality and incidence of transmural myocardial infarction

	No of patients
Operations	1 582
Operative mortality	15 (0 9%)
Perioperative infarction	94 (6 2%)

Table II Enzyme values on postoperative days 1 through 3

*SGOT (Units/liter)**	*Group with infarction (94 patients)*	*Group without infarction (1 374 patients)*
<100	1	1 279 (93%)
≧100	93 (99%)	95 (7%)
≧170	66 (70%)	43 (3%)

Normal values 8 to 33 I U /liter

Table III Postoperative mean peak SGOT values in groups with and without infarction*

	SGOT (units/liter)	
Postoperative days	*Group without infarction (95 patients)*	*Group with infarction (93 patients)*
1	124	233
2	107	189
3	88	90

Includes only patients with elevated enzyme (≧SGOT 100 U /liter) Curve is *flatter* for those without infarction

The surgical techniques for saphenous vein and left internal mammary artery bypass grafting have been described by Favaloro and colleagues[8] and Loop and associates[9]

A correlative study was made of the site of transmural infarction in relation to the zone of myocardium supplied by the grafted vessels based on the expected arterial supply to the various areas of the left ventricular myocardium[10]

Autopsy data on 11 of 15 patients who died in the hospital after operation were reviewed to determine the presence of acute myocardial infarction and the status of the bypass grafts

Follow up information was obtained by sending questionnaires to referring physicians or to patients and by reviewing the medical records of patients who returned for postoperative angiography

Results

The operative mortality and incidence of transmural myocardial infarction related to pure coronary bypass surgery are shown in Table I The 6 2 per cent incidence of transmural infarction included five patients who died with evidence of acute myocardial infarction confirmed by postmortem examination In two of these patients the bypass grafts to the zones of infarction were closed In the other three patients the grafts were patent and one of these three had emergency operation for severe left main trunk obstruction Another six patients had no evidence of acute infarction at postmortem examination Autopsies were not performed on the remaining four patients two died of stroke and two had severe left main trunk lesions

Serum enzyme and transmural myocardial infarction Of the 94 patients with postoperative transmural myocardial infarction, 93 had SGOT values of 100 or more units on one of the first three days after operation (Table II) Although these enzyme levels were highly sensitive in confirming transmural infarction, the accuracy rate was only 49 per cent (93 of 188 patients), with a substantial incidence of false positive results Even using SGOT levels of ≧ 170 units (the mean peak SGOT values in the group with infarction) the accuracy rate rose to only 60 5 per cent (66 of 109 patients) with a concomitant fall in sensitivity

Table III shows the mean peak SGOT values on the first second, and third postoperative days in the groups with and without myocardial infarction In the latter group only patients with elevated enzyme (≧ 100 SGOT U /liter) were included for comparison

Postoperative angiographic findings Table IV shows the status of the bypass grafts and postoperative left ventricular function as determined by segmental wall motion The frequency of graft occlusions was greater in the group with transmural infarction However 51 per cent of the infarction areas were supplied by patent grafts Analysis of segmental wall motion by left ventriculography performed in the right anterior oblique projection showed localized impairment of contractility in a substantial number of patients with transmural myocardial infarction In the group without infarction postoperative impairment of contractility was related to graft occlusion and progression of disease in ungrafted arteries

Improvement in contractility was noted in some patients in the group without infarction but not in the group with infarction

Clinical course in group with infarction Follow up information (Table V) was obtained in all patients with infarction after they were discharged from the hospital The minimum follow up period was 12 months (mean 26 9 months) with two deaths occurring at 2 and 8 months of follow up Almost half the patients continued to have chest pain Post hospital infarction occurred in one patient 4 months after operation Congestive heart failure was noted in four patients followed 36 to 39 months Reoperation was done in two symptomatic patients with graft failure One patient required a permanent pacemaker at 34 months for sick sinus node syndrome and lastly, one patient was confined to a long term care institution for dementia

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Intraoperative infarction is associated with an increase in mortality and morbidity The five postoperative hospital deaths in the group with infarction indicate a 5 3 per cent operative mortality rate Two subsequent deaths a few months after surgery and the development of congestive failure in four other patients could well be related to the occurrence of perioperative infarction Because almost half the patients in the infarction group has occluded grafts to vessels supplying areas of infarction graft occlusion and the attendant infarction may be a factor in the less satisfactory symptomatic improvement [1]

Table IV Postoperative angiographic findings in groups with and without infarction

	Group with infarction (45 patients)	Group without infarction† (141 patients)
Patients with at least one graft occluded	22 (49%)‡	24 (17%)
Postoperative left ventriculogram		
Unchanged	17	106
Worse	28 (62%)	20 (14%)
Improved	0	15

Includes only patients who had postoperative angiography
†First consecutive patients who returned for postoperative angiography
‡Includes only patients with occlusion of graft to vessel supplying area of infarction.

Table V Post hospital course of patients with infarction

	No of patients
No chest pain	32
Pain suggesting angina	40
Subsequent infarction	1
Congestive failure	4
Reoperation	2
Pacemaker implant	1
Dementia	1
Deaths	2
Total	83

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An evaluation of range gated pulsed Doppler echocardiography for detecting pulmonary outflow tract obstruction in d transposition of the great vessels

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Pulmonary stenosis associated with d transposition of the great vessels (d TGV) represents an important diagnostic problem Knowledge of the presence of pulmonary stenosis complicating d TGV is important because of operative and mortality considerations [1-3] The problem is further complicated by the fact that pulmonary stenosis may develop or increase in severity at any time in the course of the disease [4, 5] In many children the level and severity of the outflow obstruction can be determined by cardiac catheterization but this investigation is difficult [7] and can not be repeated as often as desired Accordingly a noninvasive test which could serially track the course of the disease would be valuable Unfortunately M mode echocardiography is not well suited to evaluation of diaphragms or rings of muscular stenosis in the left ventricular outflow tract M mode verification of noncalcified semilunar stenosis also represents a formidable problem Two dimensional echocardiographic study of the pulmonary outflow tract in d TGV offers better spatial orientation for anatomic study than M mode but the subject of its applicability for detecting obstruction of the pulmonary outflow tract in d TGV remains relatively unexplored

Recently, a range gated pulsed Doppler (RGPD) has been combined with M mode echocardiography to provide red cell velocity information in a known area of the heart [10] Additionally spectral analysis of the Doppler velocity signal is possible and should allow differentiation between laminar and turbulent flow

The purpose of the following investigation was to evaluate the accuracy of RGPD for determining the presence and site of obstruction in patients with d TGV

Methods

Our study population consisted of a random selection from the available patients with d TGV followed at Sophia Children s Hospital in Rotterdam Diagnosis of d TGV and status of the pulmonary outflow tract for this group were established previously by cardiac catheterization and angiography and in most instances were confirmed by operative visualization of the area For purposes of this study pulmonary outflow tract will refer to the area from the left ventricular outflow tract through the pulmonary artery and its right branch.

The examiners were unfamiliar with the children Each child was assigned a number and all information was collected and analyzed in a blind manner according to that number Children were studied without sedation An electrocardiograph

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Rec ved f r publ ation Oct 10 1977
Accepted f r publ ation Dec 19 1977

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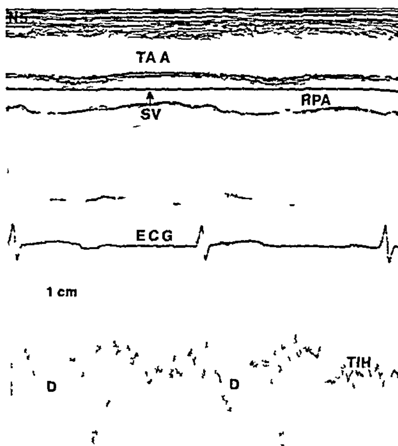


Fig 2 The sample volume (SV) is in the right pulmonary artery Mild systolic TIH dispersion is evident and the dispersion is greater than 1 cm in amplitude The general pattern of the TIH is still recognizable This was classified as disorganized (D) with pattern This child No 7 had measured pressure difference of 40 mm across the subvalvular area For abbreviations see legend of Fig 1 This sample was selected because it showed the least dispersion that was recognized by our criterion

then recorded in the pulmonary artery Finally the right pulmonary artery was located from the suprasternal notch and the Doppler information within it was recorded In each location the recording consisted of an M mode echocardiogram which indicated the site of the sample volume an electrocardiogram and a TIH During the RGPD examination an audible signal was present which represented the Doppler frequency shift This audible signal was used only to find a position in the area under investigation that was free of valve wall or septum but was usually left on during the examination

Analysis of the numbered tracings was accomplished by classifying the TIH as coherent disorganized but with pattern or noncoherent A one cm bandwidth was required to classify a pattern as disorganized or noncoherent This criterion resulted from pilot studies of normal flow patterns which showed no bandwidths greater than 7.5 mm Examples of each pattern are shown in Figs 1 to 3 Each patient s record was judged independently by two observers Results of each observer were then coded with the examination number The code was then broken by matching the TIH results to the previously established diagnosis

Results

Twenty one children comprised the original group One was excluded because of lack of cooperation Another was excluded because the status of the outflow tract was uncertain at time of catheterization. A third child was excluded because of a Pott s anastomosis Reason for this exclusion will be later discussed An adequate examination was possible in each of the remaining 18 children Average examination time was 15

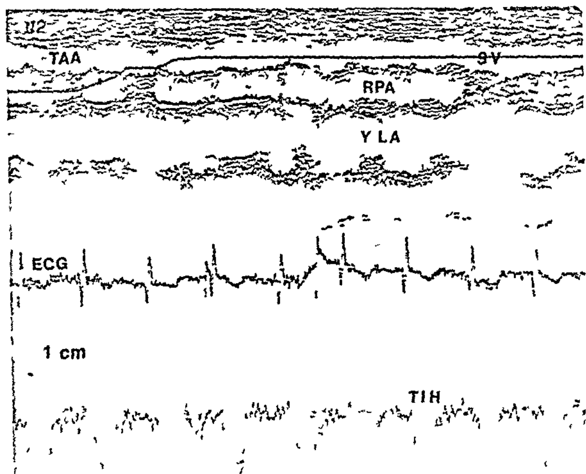


Fig 1 This suprasternal notch study sample was from patient No 15 who had no obstruction of the pulmonary outflow tract The example shows time interval histogram (TIH) during a sweep from the right pulmonary artery (RPA) to the transverse aortic arch (TAA) Each dot represents the average frequency of reflections during 1/4 000 of a second In this instance the dots are relatively coherent No dispersion consistently exceeds 1 cm The beats before under and to the right of the label TIH show increased dispersion during deceleration as compared to acceleration Transient RPA disturbance in beat 1 is artifact and not repeated in beat 2 SV = sample volume YLA = left atrium viewed in the Y axis

ic lead was recorded for time reference Instrumentation consisted of an ATL 500A* and a Honeywell 1856 recorder This instrument package includes a second generation time interval histogram (TIH) output the theory of which is covered elsewhere [11] The second generation TIH differs from the first in improved precision of the output A 3 Mhz transducer provided both Doppler and M mode signal The echo Doppler examination of the pulmonary outflow tract was conducted in a manner similar to the standard pediatric M mode examination except as noted The pediatric examination from the suprasternal notch was performed after the method of Allen and co workers [12] The Doppler signal could be sampled from any site along the echo beam by the range gating feature and the sampling site was depicted by a marker on the standard M mode tracing This sampling site an area of about 2 × 4 mm is called the sample volume The threshold was set to low noise setting, line level was set to demonstrate positive peaks on the line level indicator and baseline was set in the noncompressed state The sample volume was placed between the septum and anterior mitral valve leaflet to record Doppler information in the left ventricular outflow tract In each instance the recording objective was to find a normal TIH If an abnormal TIH remained after considerable effort to find a normal one the abnormal TIH was accepted as a representative of that area The search, in effect was seeking to find a place in which a valve wall or septum did not pass into the sample volume for such passage causes a signal which would create confusion in later analysis After recording the left ventricular outflow tract signal the transducer position was changed so that the area at the tips of the pulmonary leaflets or the area just above them was sighted by M mode The Doppler signal was

*Advanced Technology Laboratory Bellevue Wash. U S A

Table I Comparison of echo Doppler and actual diagnosis

Patient	Age	Doppler		True diagnosis of Pulm outflow tract	Most recent evaluation procedure	Doppler assessment	
		LVOT	Pulm Art			Right	Wrong
1	1	N	N	No obstruction	Operation	x	
2	13	N	+	51 mm pulm valv stenosis	Catheterization	x	
3	13	N	N	No obstruction	Operation	x	
4	9	+	+	Subvalv stenosis and pulm banding	Operation	x	
5	9	N	N	No obstruction	Operation	x	
6	7	+	+	40 mm subvalv stenosis	Catheterization	x	
7	3	+	+	40 mm. subvalv stenosis	Operation	x	
8	9	N	+	84 mm valv stenosis	Operation	x	
9	5	N	N	No obstruction	Operation	x	
10	6	N	N	No obstruction	Operation	x	
11	4	N	+	Hypoplastic pulm with obstr post valvotomy	Operation	x	
12	7	N	N	No obstruction	Catheterization	x	
13	11	N	N	No obstruction	Catheterization	x	
14	15	N	N	No obstruction	Catheterization	x	
15	9	N	N	No obstruction	Operation	x	
16	2	N	N	No obstruction	Operation	x	
17	6	+	+	130 mm gradient subvalv stenosis not resected	Operation	x	
18	8	N	+	No obstruction	Catheterization		x

N = no detectable turbulence + = turbulence detected.
No obstruction means no pressure difference across any portion of the outflow tract measured that exceeded 10 mm Hg at catheterization or no detectable narrowing of the outflow tract at direct operative examination

efficacy in detecting obstructions to pulmonary outflow in d TGV This is not surprising for these obstructions frequently occur in a portion of the heart that has considerable superior-inferior motion and they are difficult to track by single crystal M mode echo In nontransposition subaortic diaphragms the only direct finding may be an unidentified line in the outflow tract that is difficult to separate from artifact In others findings may be absent Indirect findings have also been reported Moreover semilunar stenosis in children has remained a difficult diagnostic problem from M mode echo However one common factor for each type of obstruction is production of nonlaminar flow A flow disturbance can be identified by spectral analysis of the Doppler signal and this formed the rationale for this study

Detailed echo Doppler theory is covered elsewhere[19] Briefly the ultrasound is scattered when it strikes red cells moving within the blood stream The frequency shift can be sensed and velocity information can be recovered

The magnitude and direction of this frequency shift depend upon the direction of motion of the scattering particles and the angle between the sound beam axis and the vector direction of motion Accurate calibration of velocity requires knowledge of this angle but this information is not usually available Thus quantitation is not usually possible but qualitative assessment is possible

Although the best echocardiographic signal is obtained when the structure is at right angles to the ultrasound beam the reverse is true for the Doppler signal It is maximized when it is least perpendicular to the motion of the scattering particles Thus the optimal echo and optimal

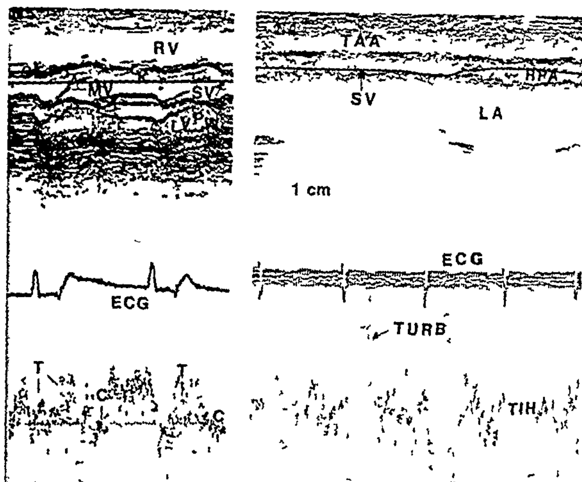


Fig 3 The sample volume is in the left ventricular outflow tract *in the left panel* (*RV* = right ventricular cavity *SEPT* = septum *MV* = anterior mitral valve leaflet *LVPW* = left ventricular posterior wall) A systolic flow disturbance exceeding 1 cm amplitude is apparent and marked *(T)* The pattern although not smooth in diastole has coherence *(C)* and frequency dispersion in diastole does not exceed 1 cm *The right panel* shows marked frequency dispersion in systole with coherent in diastole This patient No 6 has subvalvular pulmonary stenosis For abbreviations see legend for *Fig 1* Calibration is similar in both panels

minutes Subjects ranged in age from 12 months to 13 years The two observers classified the selected patterns identically However no finer gradation than the three described patterns was attempted

Eleven of the children had normal pulmonary outflow tracts (Table I) Ten of these were correctly classified by RGPD technique and criteria that were applied One child with a normal valve at pre and postoperative catheterization at operation was misclassified The reason for misclassification was not apparent

Seven of the children had pulmonary stenosis (four valvular, three subvalvular) (Table I) In each instance the presence and site of the first obstruction was correctly identified One child (No 4) had more than one level of obstruction The second level, at the pulmonary artery could not be differentiated from the first which occurred at the subvalvular level

Although two patterns of disturbance were present (noncoherent and disorganized) both were classified merely as abnormal since no data exist to prove that they indicate a different origin

Discussion

Obstruction to the pulmonary outflow occurs in approximately 20 per cent of children with d TGV [13] Although the different types of obstruction are numerous, they can be generally classified as subvalvular, valvular, or supravalvular This classification is functional for purposes of Doppler evaluation, for the individual lesions are recognized only by their location Nevertheless the presence of these malformations is of critical importance due to their increased risk [14] Many can be corrected at operation and others can be palliated if their presence is known

Although a few cases of pulmonary outflow obstruction have been observed by echocardiography [15] conventional M mode echo has no proven

exclude this child from the results The child had evidence of an abnormal pulmonary artery TIH but the origin could not be determined by the Doppler examination However the area under the valve could be studied in this instance This problem presents an important limiting factor for the Doppler examination

Echo-Doppler appears to be a promising technique which has the capability of providing information in many areas other than the one described in this report[21-27] However the present technical and inherent problems create important limitations but should not detract from further investigations of its utility

Summary

The aim of this study was to determine the accuracy of range gated pulsed Doppler (RGPD) echocardiography for detecting obstruction to the pulmonary outflow tract in children with d transposition of the great vessels (d TGV) Twenty one children were randomly selected for those available with d TGV and were studied by precordial and suprasternal RGPD echocardiography Three were excluded leaving a population of 18 subjects The exclusive criterion used to judge the RGPD results was the output of the time interval histogram (TIH) Coherence of the TIH was considered to represent laminar flow Dispersion of the TIH was considered evidence of flow disturbance and obstruction to the outflow tract With the range gating feature the first site of disturbance could be localized Information was handled by a technique that decreased bias RGPD results were then compared to diagnoses of the outflow tract established at cardiac catheterization or operation Comparison of these results indicated that all seven children with obstruction were correctly identified by RGPD study and the level of the first obstruction was correctly identified With one exception all children without pulmonary obstruction were correctly identified by the examination

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Doppler signal cannot usually coexist, and a tradeoff must take place The usual tradeoff is a degraded but recognizable M mode signal

In laminar flow with a relatively flat velocity profile, blood cells passing through the Doppler sampling volume will have nearly the same velocity and direction The output signal at any instant in time will have a narrow bandwidth frequency shift and this can be appreciated by spectral analysis or, to a less precise extent, by listening to the nearly pure tone produced by passing the Doppler shifted frequency into an audio amplifier and speaker In the case of disturbed flow the scattering particles simultaneously have multiple velocities and directions The disturbed flow may be turbulent but no way exists with the Doppler to prove actual turbulence, so the term 'disturbed flow' will be used instead Disturbed flow causes the Doppler frequency shift to have a greater bandwidth and produces a more randomly composed sound The audible characteristics may be learned but are difficult to evaluate in a standarized objective manner Rapid spectral analysis and fast Fourier transforms are possible but not yet available for real time use with this instrumentation However, a TIH output, which closely approximates the result of other types of analyses is available and translates the Doppler output into a form which can be graphically recorded [20]

No technique has been developed to measure the dispersion of the TIH, thus it must be evaluated in a manner that is not entirely quantitative We chose to classify tracings as coherent noncoherent and disorganized The first two are simple to separate but the third is more qualitative It was defined as a pattern which was more disorganized than usual and had an amplitude of 1 cm or more but not random An electronic dispersion measuring technique would be an improvement over this classification

The population had been previously studied and their diagnoses were established by pressure recording across the area of interest at cardiac catheterization, angiography, and in most cases, results were confirmed by direct observation and examination of the pulmonary outflow tract at operation The objective of this investigation was to separate those children with pulmonary outflow obstruction from those without obstruction Results indicate that this was usually possible with the described techniques and criteria One misclassification occurred and the reason for this is not obvious, as the examination and record were both acceptable

The method used to establish the true diagnosis is not ideal Perhaps the best confirmation would be passage of a transducer catheter through the area of interest just prior to RGPD examination but this was neither practical nor justifiable The surgeon's evaluation at operation by direct visualization and examination or a postoperative catheterization with pressure measurement with a hydraulic catheter system across the area of interest or both were accepted as valid If a child had neither evaluation, or if one was in question that individual s results were excluded

The close agreement between examiners for spectral patterns is not unexpected The areas studied produce strong Doppler signals and are among the simplest to classify Other areas of heart may prove more difficult

Although the results are encouraging the technique requires further study and development The examination is not simple The sample volume (2 × 4 mm) at 3 Mhz is relatively large for small children The sample size can be decreased by increasing the echo-Doppler frequency, but this change decreased penetration Additionally, the sample volume must be set at a selected depth but the cardiac structures are in motion and tend to intercept the stationary sample volume This causes artifactual dispersion of TIH Much time was expended in finding a place in a chamber in which the sample volume was free within the cavity during the entire cardiac cycle Finally, the echo signal used as a locator for the sample volume is necessarily degraded in order to obtain a useful Doppler signal These are principally technical problems which may have solutions A more difficult nontechnical problem relates to the accurate classification of the situations in which two levels of obstruction are in close physical proximity to one another Once a flow disturbance is created in a system as small as the heart or great vessels it does not quickly dissipate Thus a disturbance produced by a distal obstruction could be masked by one produced at a proximal location In a similar manner a disturbance produced by a systemic-pulmonary artery shunt could mask one produced by a nearby obstruction This problem was encountered in the investigation with a child who had a Pott s anastomosis and led us to

Blood pressure levels in acute myocardial infarction

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The concept of salvaging ischemic myocardium in patients with acute myocardial infarction by reducing left ventricular afterload has become an applied reality with the development of indications for intervention and the use of many agents including antihypertensives.[2] The level of systemic blood pressure has been used as a monitor of afterload, primarily because it is easy to measure either directly or indirectly, and may be serially recorded as a marker for assessing the efficacy of therapeutic intervention. It is important if such a measurement is to be used to know more of the apparent natural history of blood pressure levels in the hospital setting, especially in the early stages of admission for cardiac pain suspected to be due to acute MI; such is the purpose of this study. It is certainly correct that no patient in these circumstances is allowed a truly natural course since there are many variables, iatrogenic and otherwise, which alter the hemodynamic state. Nevertheless a realistic definition of the trends to be expected should result from such an investigation.

Material and methods

Prospective data were obtained from a group of 1,000 patients admitted successively to a Coronary Care Unit; of these 623 had chest pain which was diagnosed as cardiac in origin using previously established criteria. Those included in the study were aged 65 or less, admitted to the hospital within 6 hours of the onset of chest pain, were not in cardiogenic shock, and were not given specific antihypertensive or unloading therapy. They comprised 112 patients (95 male, 17 female) with acute myocardial infarction (AMI) and 96 patients (79 male, 17 female) ultimately diagnosed as having angina due to cardiac ischemia without clinical evidence of myocardial necrosis. Serial sphygmanometric blood pressures were taken by specially trained nursing staff from the time of admission over a period of 72 hours. During the first 24 hours in hospital, blood pressures were recorded at least hourly. The diastolic cut off point was the absence of sounds (Korotkoff phase 5). Initially the blood pressure in both arms was taken and the arm with the highest diastolic pressure was selected for serial measurement. Cuff width was 14 cm unless the arm diameter warranted a larger size. Blood pressures taken during the course of major arrhythmias were not included in the data. Ventricular standstill, ventricular fibrillation, ventricular tachycardia, supraventricular tachycardia, atrial flutter, atrial fibrillation, and second and third degree AV block were all considered major arrhythmias. Class II and Class III (Killip) were used to define patients in cardiac failure.[3]

Patients with angina were included because it is not possible in the early stages of their clinical course to rule out the diagnosis of acute myocardial infarction conclusively; accordingly they might be considered for antihypertensive treatment aimed at myocardial sparing. In addition, since they did not have clinically determined myocardial injury, they constitute a control group with an environmental and emotional commonality.

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Received for publication Oct. 13, 1977.
Accepted for publication Jan. 13, 1978.

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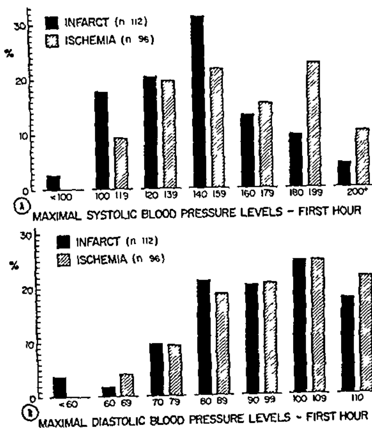


Fig 1 Maximal systolic and diastolic blood pressure levels (mm Hg) recorded in the study population during first hour of hospital admission

Results

First hour blood pressure During the first hour of hospitalization mean systolic blood pressure (SBP) for the whole cohort was 150 2 (± 30 7) *mm Hg A SBP ≥ 160 mm Hg* was present in 81 patients (38 9 per cent) Mean diastolic blood pressure (DBP) was 92 1 (± 18 7) mm Hg and a DBP ≥ 100 was present in 88 patients (42 3 per cent) The range of maximal blood pressure (BP) readings is shown in Fig 1 These data show that in acute myocardial infarction (AMI) SBP appears unimodal with a shift to the left and that in cardiac ischemia SBP demonstrates bimodality due to the number of patients with SBP 180+ The DBP levels tend to parallel each other for cardiac ischemia and AMI with a shift to the right

Table I shows mean BP levels by diagnosis and sex Men and women with angina have a significantly higher mean SBP than those with AMI This also applies to DBP in women Women have higher mean SBP than men for both cardiac ischemia and AMI but this is not a statistically significant difference This also applies to DBP in women with cardiac ischemia

If the criterion for unloading therapy was set at a BP 140/90 then 93 (44 7 per cent) of the total group would qualify during the first hour of admission If it were set at 160/100 or greater then this number would be 66 (31 7 per cent)

Table I Initial (mean and SD) blood pressure levels (mm Hg) in acute myocardial infarction and cardiac ischemia

	Total	*Men*	*Women*
AMI	(n = 112)	(n = 95)	(n = 1[illegible])
Systolic	143 2 ± 28 7	140 9 ± 26 7	156 5 ± 36 3
Diastolic	90 2 ± 18 9	90 4 ± 19 5	88 9 ± 15 9
Ischemia	(n = 96)	(n = 79)	(n = 1[illegible])
Systolic	158 3 ± 31 1	154 7 ± 31 3	174 9 ± [illegible]4 6
Diastolic	94 3 ± 18 3	93 5 ± 16 4	103 3 ± 1[illegible]0

Changes in blood pressure during first 6 hour period BP changes during the first six hours were evaluated since it is during this time that BP lowering may be considered or, if in effect monitored By the sixth hour SBP mean for the group had fallen from 150 2 to 130 1 (± 24 0) mm Hg and DBP from 92 1 to 81 3 (± 15 5) mm Hg The 93 patients with an initial first hour BP of 140/90 were evaluated and the data are shown in Fig 2 Only 23 patients (24 7 per cent) were still in the range by the sixth hour with the major fall occurring within 3 hours This is 11 1 per cent of the total cohort Separation of the data by diagnosis showed no statistically significant difference in BP behavior between AMI and cardiac ischemia The 66 patients with an initial 1 hour BP of 160/100 or more demonstrated similar striking falls in BP by 6 hours At that time only 13 (19 7 per cent) remained with such a BP elevation This is 6 3 per cent of the total cohort Again there was no significant difference in behavior between AMI and cardiac ischemia It was also not possible to separate out this group with persistent hypertension by any clinically predictive means

Changes in blood pressure during the first 72 hour period During the 18 hours following the first 6 hours 21 patients (10 5 per cent) had at least one blood pressure reading of 160/100 or more Only eight developed this de novo and in five this was associated with return of chest pain

Fig 3 shows the percentage of patients with certain defined levels of BP fluctuation for systole and diastole during the first 24 hour period The degree of change can be seen to be

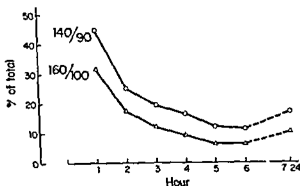


Fig 2 Percentage of study population with blood pressure levels greater than 140/90 mm Hg and 160/100 mm Hg or more recorded during the first six hours and from 7 to 24 hours of hospital admission

considerable in the majority of patients and such fluctuations were with very few exceptions due to a sequential fall rather than a rise in level A mean fall in SBP in the region of 50 mm Hg (cardiac ischemia 52.2 AMI 49 0) and a mean fall of approximately 30 mm Hg in DBP (cardiac ischemia 32 4 AMI 34 0) took place (Table II) A sex difference in mean SBP was apparent since women with AMI or cardiac ischemia had a greater fall

Fig 4 shows the fall in the number of patients with certain BP levels during a 3 day period There is a consistent pattern for both SBP and DBP fall in patients with cardiac ischemia and AMI By the third day those patients who had the higher BP readings of 160 systolic or more and 100 diastolic or more were few This group did not consist of only those patients who had persistent hypertension but also included those who had any isolated reading which was above the levels set Only two patients with AMI had persistent hypertension (BP 160/100 or more) during the first 72 hours.

Clinical course of patients with acute myocardial infarction A number of clinical variables were examined in order to determine differences between hypertensive patients (BP 160/100 or more) and non hypertensive patients during hospitalization (Table III) The only statistically significant difference was in the incidence of supraventricular tachyarrhythmias in non hypertensive patients Trends were present suggesting that heart failure higher degrees of AV block and sinus bradycardia were more common in the non hypertensive group The last two features might be explained by a higher incidence of inferior myocardial infarct (48 1 per cent) in this group when compared to the hypertensive group (22 6 per cent)

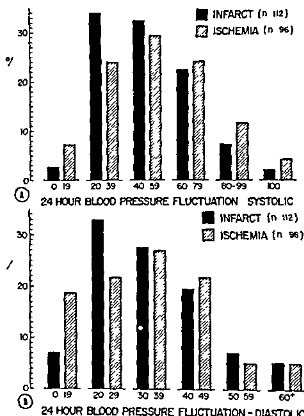


Fig 3 Maximal systolic and diastolic blood pressure fluctuations over first 24 hours of hospital admission grouped by degree

Discussion

This study was done to quantify what has been for decades a common clinical observation to wit that elevated blood pressure is often found in patients admitted to hospital with acute myocardial infarction Data are available on long term follow up of such hypertensive patients[9] and prognostic indices related to initial blood pressure recorded in hospital[1-11] have been developed Hypotension is established as an index of poor prognosis but there is controversy concerning the role of hypertension The short term data mostly indicate that the presence of an elevated blood pressure has no significance prognostically However Fox and colleagues[1] found that the mortality rate incidence of cardiac failure major arrhythmias and mean peak SGOT were significantly greater in a group of patients with a

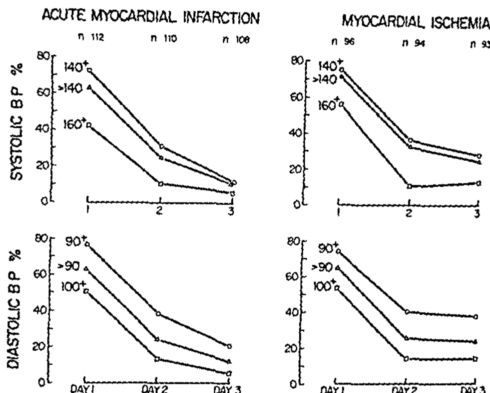


Fig 4 Percentage of patients with acute myocardial infarction and cardiac ischemia at specified levels of systolic and diastolic blood pressure by hospital days 1 to 3 (24 hour periods) Terminal digit preference is apparent for diastolic blood pressure levels of 90 mm Hg or more (90+) compared to greater than 90 mm Hg (> 90) It is present but less apparent for systolic blood pressures of 140+ mm Hg compared to > 140 mm Hg

Table II Fluctuation (mean and SD) over 24 hours of blood pressure (mm Hg) in acute myocardial infarction and cardiac ischemia

	Total	*Men*	*Women*
AMI	(n = 112)	(n = 95)	(n = 17)
Systolic	49 0 ± 20 2	47 1 ± 19 3	60 3 ± 21 4
Diastolic	34 0 ± 15 1	34 4 ± 15 4	31.8 ± 13 2
Ischemia	(n = 96)	(n = 79)	(n = 17)
Systolic	52 2 ± 24 3	49 4 ± 24 0	65 1 ± 22 4
Diastolic	32 4 ± 14 1	30 9 ± 12 8	39 2 ± 17 9

systolic blood pressure of at least 170 mm Hg on admission to hospital

Since blood pressure elevation is a possible marker for unloading therapy in the early stages of acute myocardial infarction, it was appropriate to measure this serially in a defined population By this means the usefulness of such measurements in the management of acute myocardial infarction might be established This could be especially important if hemodynamic data were lacking and simple clinical findings were all that might be available to make decisions on unloading therapy

The results indicate that initial blood pressure elevation is common and, depending on the criteria used, is present in 30 to 40 per cent of patients with acute myocardial infarction not in cardiogenic shock The more dramatic finding was the lability of this hypertension, since a considerable fall in blood pressure occurred very early on in the clinical course, so that by six hours after hospital

Table III Comparison of selected variables between hypertensive and non hypertensive patients with AMI

	Total (n = 112)	*Hypertensive (n = 31)*	*Non hypertensive (n = 81)*
Mortality	10 (8 9)	3 (9 7)	7 (8 6)
Heart failure	42 (37 5)	8 (25 8)	34 (42 0)
VF VT	23 (20 5)	5 (16 0)	18 (22.2)
2° 3 AV block	17 (15 2)	2 (6 5)	15 (18 5)
SV tachycardia	20 (17 9)	2 (6 5)	18 (22.2)†
Ventricular ectopics	82 (73 2)	24 (77 4)	58 (71 6)
Sinus bradycardia	45 (40 2)	8 (25 8)	37 (45 7)
Sinus tachycardia	55 (49 1)	14 (45 2)	41 (50 6)

Percentages in brackets.
11 (9 8) primary in CCU
†$P < 0.05$
‡VF = ventricular fibrillation VT = ventricular tachycardia SV = supraventricular

admission the number of hypertensive patients has fallen to 6 to 10 per cent The number of patients with persistently elevated blood pressure over 24 hours is very small Women with acute myocardial infarction and cardiac ischemia are more likely to have higher initial blood pressure readings than men and to be equally labile

The etiology of hypertension in acute myocardial infarction is speculative It is easy to attribute it to anxiety and stress with increased catechol release This has been studied in the past and catechol levels do roughly correlate with blood pressure [8] We found a remarkably similar blood pressure course in patients with acute myocardial infarction or cardiac ischemia suggesting that a psychic response to environment or chest pain may be the common denominator In addition a homeostatic hemodynamic response to a decreased cardiac output might be considered with possibly an overshoot phenomenon Little is known concerning the initial somatic reaction to myocardial injury although evidence for enhanced autonomic activity is frequently present in the early stages Furthermore a previously hypertensive or hyper reactive patient might respond differently to stress The identification of such patients admitted to a Coronary Care Unit is difficult since many have not had blood pressure recordings taken in the past and it is unrealistic to attempt to separate out such a group There are experimental and clinical data suggesting that an initial hypertensive or pressor response in the early stages of acute myocardial infarction may be protective against ventricular fibrillation and sudden death [9, 6]

The rapid fall in blood pressure must also be considered Heart failure is common in the early stages of acute myocardial infarction and cardiac output may fall without much change in other factors determining blood pressure Inappropriate use of diuretics at this stage could lead to hypovolemia with diminution of effective circulating volume In the Coronary Care Unit sedatives and narcotics are often used to allay patient fear and pain This therapy could contribute to such a fall It could be that the simplest unloading therapy in early uncomplicated AMI is reassurance meticulous attention to relief of pain and adequate sedation

This study has demonstrated in a more objective fashion the type of changes that are to be expected in blood pressure in a group of patients with acute myocardial infarction It is important to understand the constraints that apply to any investigation requiring indirect blood pressure measurement and these have been well reviewed by Rose Holland and Crowley [11] Although methodology was standardized and sphygmanometers were carefully maintained blood pressures were taken by several individuals thus leading to the possibility of well defined areas of inaccuracy Without an automatic blood pressure monitoring system it is very difficult to eliminate both observer prejudice and terminal digit preference Terminal digit preference did occur in this study as seen by a disproportionate number of zero readings

It was also difficult to control the number of variables that could exist in such a clinical situation All patients were at bed rest during the observed period and standard protocols were used for treatment However in a Coronary Care Unit most drugs used have effects on blood pressure levels and even sleep [8] or the administration of oxygen[19] may alter blood pressure levels It was not possible to account for or eliminate all the variables that may exist under these circumstances and this has to be taken into considera tion when evaluating our data

We would conclude that blood pressure levels although easily obtained are too labile a measurement in acute myocardial infarction for use in the first few hours as a marker for unloading manipulation whether for initiation or maintenance Furthermore hypertension on admission to hospital did not worsen prognosis in our patients

Summary

Serial blood pressure recordings were taken for 72 hours in 112 patients with acute myocardial infarction and in 96 patients with cardiac ischemia admitted to hospital no more than 6 hours after the onset of chest pain During the first hour of admission 66 (31 7 per cent) had a blood pressure recorded 160/100 or greater By the sixth hour without specific antihypertensive therapy this number had fallen to 13 (6 3 per cent) This fall was subsequently maintained with very similar trends for both acute myocardial infarction and cardiac ischemia Such an early blood pressure fall in acute myocardial infarction may indicate that this is too labile a measurement to determine the need for or efficacy of antihyper

tensive therapy aimed at the preservation of myocardium The hospital course and mortality rate of patients with acute myocardial infarction and early hypertension, as defined, did not differ significantly from the non hypertensive group

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The effect of aging on ventricular contractile performance

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Recent studies using canine ventricular trabeculae have shown that maturation is associated with a significant improvement in contractile performance [1, 2] Few studies most of them carried out in rats have attempted to assess the changes in contractility that occur later in life with the aging process [3, 5] Since the reported results are not only conflicting but the conclusions sometimes diametrically opposed [5] we decided to study the contractile performance of canine right ventricular traebeculae at ages comparable to human adulthood and senescence

Method

Sixteen mongrel dogs weighing 16 to 18 kilograms and of either sex were anesthetized with sodium pentobarbital (30 mg /Kg) administered intravenously Two age groups were studied The first group was composed of nine dogs 36 ± 4 weeks of age or about 9 months The second group included seven old dogs free from parasitic disease that a veterinarian estimated to be at least eight years of age Each dog had poor teeth and cataracts but its nutritional state showed no obvious deterioration None had evidence of cardiac disease or congestive heart failure The entire heart was rapidly removed and placed in a beaker of Krebs Ringer s bicarbonate solution that was continuously bubbled at 37° C with a 95 per cent O_2 5 per cent CO_2 gas mixture The bathing solution contained (mmoles/liter) Na 145 K 4 2 Ca^{2} 1 25 Mg^{2} 1 2 Cl 125 SO_4^{2} 1 2 H PO 2 4 HCO_3 25 and glucose 5 6 The same continuously oxygenated and stirred solution was subsequently utilized for isolated muscle superfusion After equilibration the solution had an oxygen tension (PO_2) of 550 mm Hg or greater and a pH of 7 40 ± 0 02

Ventricular trabeculae were isolated from the same regions of the right ventricle as previously described [1] Each muscle was then mounted in a myograph* with one end of the muscle attached to a fixed force gauge that has no measurable nonlinearity in the tension signal over applied forces up to 10 g The other end of the muscle was attached to a light aluminum pendulum for a determination of length changes Positional changes of the length lever were sensed by a linear differential transformer whose small iron core was firmly attached to the lever The equivalent mass of the lever was 0 3 g which has negligible effect on muscle characteristics Displacements of up to 10 mm showed no measurable nonlinearity in the length signal The frequency responses for both systems was determined and was found accurate up to 100 Hz The compliance of the tension transducers and the lever system combined was less than 0 5 μ per gram. An adjustable micrometer which restrained the lever movement was used to set the muscle lengths Along the lever a small wire carrying electrical current in a magnetic field generated the desired forces (load on muscle) to hold the lever against the micrometer

Outputs from the force and length gauges along

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This work was supported by the N tional H art Lung and Blood Inst t te (Program Project Grant HL 11,310 and SCOR on Ischemic H art Disease No. 1 P17 HL 17 667) a d by the Ra t Fund f r Medic l Rese rch.

Received for publication Dec. 19 1977

Accepted f r publication J n 25, 1978

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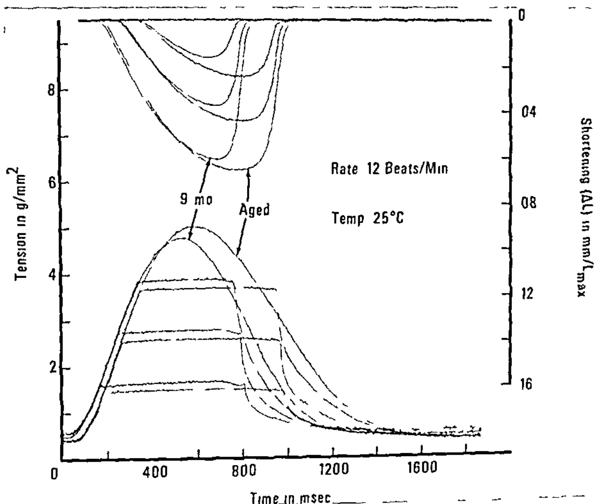


Fig 1 Record illustrating the difference in contractile performance in a 9 month old and a > 8 year old ventricular trabeculae Tension is inscribed from bottom to top whereas shortening is inscribed from top to bottom

Table I Values from the length-tension curves obtained in 16 canine right ventricular trabeculae at L_{max}

Age	*Weight (mg)*	*Length (mm)*	*Cross sectional area (mm)*	*Resting tension (G /mm)*	*DVLP (G /mm ²)*	*MRTR (G sec /mm ²)*	*TLAT (msec)*	*TMRT (msec)*	*TMXT (msec)*	*DRTN (msec)*	*TRLX (msec)*
9 Months	6 27	5 85	1 01	0 375	4 503	15 13	81 9	239 7	574 0	1284 2	710 9
(n = 9)	±3 16	±1 28	±0 35	±0 079	±0 545	±2 86	±19 5	±46 7	±73 8	±136 6	±122 6
>8 years	5 98	6 50	0 87	0 488	4 566	12 31	98 1	283 8	689 6	1768 8	1077 4
(n = 7)	±3 24	±0 75	±0 46	±0 202	±0 385	±1 89	±23 6	±55 4	±149 6	±617 6	±499 7
t	0 17	1 12	0 65	1 31	0 24	2 11	1 41	1 24	1 89	2 14	1 99
p	NS	NS	NS	NS	NS	p < 0 05	p < 0 10	NS	p < 0 05	p < 0 025	p < 0 05

DVLP = maximum developed tension MRTR = maximum rate of tension rise TLAT = latency time TMRT = time to maximum rate of tension rise TMXT = time to maximum tension DRTN = duration of contraction and TRLX = relaxation time calculated by substracting time to maximum tension from duration of contraction NS = not significant (P < 0 05)

with the stimulus signal were sent through an A/D converter to a PDP 7 computer The computer then signaled through a D/A converter back to the apparatus to control loading of the muscle Prior to each isometric tension series the computer recalibrated the tension transducer if necessary The contractions were then registered and the following data were routinely calculated and recorded on digital tape the length and tension signals at 1 000 samples per second resting tension developed tension (peak developed isometric tension at L_{max}) maximum rate of tension rise maximum change in length maximum velocity of shortening latency time (defined and measured as the interval between the onset of the stimulus and the point at which the developed

tension reached 2 per cent of its maximum value) time to maximum tension time to maximum rate of tension rise time to maximum shortening time to maximum velocity of shortening and relaxation time The cross sectional area was estimated at L_m (the length of the muscle at which developed tension was maximum) by dividing the weight of the muscle by its length This value was then utilized as the normalizing factor for the tensions

After being mounted the muscles were first allowed to shorten with a preload equivalent to approximately 50 per cent of the resting tension subsequently observed at L_m After about 2 to 3 hours length-tension curves were then obtained for the next 24 hour period during which each experiment was performed there was no significant further increase or decrease in peak isometric tension In every experiment after each incremental change of initial muscle length 5 minutes were allowed to elapse before the data were recorded. This procedure was adopted to minimize the effect of stress relaxation Temperature was kept constant (25 0 ± 0 1° C) through a feedback controlled Peltier junction

All preparations used were quiescent unless stimulated Unless otherwise indicated each muscle was stimulated 12 times per minute by square wave pulses delivered to plate electrodes from a Grass stimulator Stimulus duration was 5 msec and the voltages used were 10 per cent above threshold All results are expressed as means ± 1 SD The significance of differences was assessed by Student s t test the comparison of regression lines was done by a standard technique[7]

Results

Contractile performance of normally mature and of old right ventricular trabeculae

Isometric variables Table I summarizes all the data obtained at L_m in 16 muscles isolated from the same region of the right ventricle of dogs 9 months (n = 9) and more than 8 years (n = 7) of age Weight length cross sectional area resting tension and developed tension were the same Old age however was associated with a definite decrease in maximum rate of tension rise (−18 per cent) and a significant increase in total twitch duration (+38 per cent) There was no concomitant change in the latency time Relaxation time increased proportionally far more (+52 per cent) than the time to maximum tension (+20 per

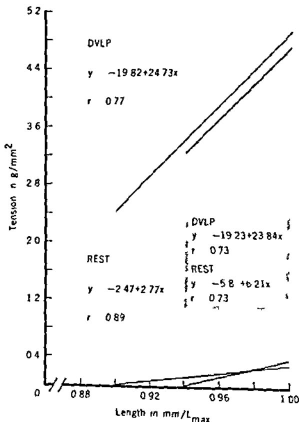


Fig 2 Two length-tension curves of right ventricular trabeculae at 9 (n = 9) months of age and > 8 years (n = 7) old (*shaded area*) The two diagrams represent the linear regressions of all data points collected The equations for DVLP (developed tension) and REST (resting tension) in the shaded area are those of the older muscle group There is no significant difference between tensions developed in the normally mature and old muscles (upper set of regression lines) In contrast passive stiffness up to L_m (= 1 00) is significantly greater in the older muscle

cent) indicating that slowing of individual twitches was mostly due to a profound prolongation of the relaxation phase (Fig 1) Fig 2 illustrates the linear regressions of the two length tension diagrams plotted from all the data collected in those 16 ventricular trabeculae Whereas the developed tensions remained virtually unchanged between the period of normal maturation (9 months) and old age (over 8 years) the resting tensions underwent a remarkable transformation Both the slope and the x intercept changed significantly with aging Whereas the L_o in the adult muscles averaged 0 901 ± 0 014 mm /L_m that of the old muscles increased to as much as 0 940 ± 0 024 mm /L_m This difference was significant at a $p < 0.001$ level Although the resting tensions at L_m were virtually identical in the younger and older

Table II Values from the force–muscle shortening relationships obtained in 16 canine right ventricular trabeculae at L_{max} and constant afterload (1 g)

Age	Weight	Length	Cross sectional area	Resting tension (G/mm²)	DLTL (mm/L_m)	MAXV (mm sec⁻¹/L_m)	TLAT (msec)	TMXV (msec)	TMXS (msec)	DRTV (msec)
9 Months	6.27	5.85	1.01	0.405	0.085	0.264	85.0	263.3	718.2	1068.7
(n = 9)	±3.16	±1.28	±0.35	±0.103	±0.014	±0.061	±19.4	±42.0	±85.1	±13[illegible].3
>8 years	5.98	6.50	0.87	0.476	0.077	0.204	104.6	290.0	930.1	1388.4
(n = 7)	±3.24	±0.75	±0.46	±0.178	±0.014	±0.051	±24.5	±76.2	±23[illegible].5	±401.0
t	0.17	1.12	0.65	0.94	1.68	2.00	1.67	1.11	2.37	2.09
p	NS	NS	NS	NS	p < 0.10	p < 0.05	p < 0.10	NS	p < 0.0[illegible]	p < 0.0[illegible]

DLTL = maximum muscle shortening MAXV = maximum velocity of shortening TMXV = time to maximum velocity of shortening and TMXS = time to maximum shortening

muscles an analysis of the respective slope of those passive tensions indicated that the difference was statistically significant at the $p < 0.05$ level

Isotonic variables Table II is a summary of all the data collected When studied and compared at the same initial muscle length and constant afterload of 1 g the extent of shortening in young and old muscles (Fig 1) was quite comparable However there was a significant difference in their respective v intercepts ($p < 0.05$) Fig 3 depicts the force extent of shortening relationships, further illustrating that the amount of shortening did indeed decrease with aging Fig 4 and Table II demonstrate that the maximum velocity of shortening was significantly reduced in the older muscles (−23 per cent) In addition time to maximum shortening as well as time to maximum velocity of shortening were also prolonged (+30 per cent and +14 per cent respectively) Total twitch duration was prolonged by as much as 30 per cent

Discussion

There is little question that the efficiency of cardiac performance tends to decrease with age Both heart rate[9] and cardiac output[9,10] are significantly decreased in the elderly In our study the strength of myocardial contraction was little affected by aging but the extent of shortening tended to decrease However the rate of rise of tension and the velocity of shortening were both definitely diminished in the older muscles Compared to 3 and 9 months old ventricular trabeculae[1,2] the duration of each individual twitch in older muscles was distinctly prolonged On closer analysis the depression of the time dependent parameters was far from uniform At one extreme the latency time remained unchanged, whereas at the other extreme relaxation time underwent the most profound prolongation Taken collectively all these observations indicate that canine right ventricular muscles lose speed *but keep their strength with aging* Furthermore it appears that increased duration in relaxation time might represent an early and sensitive indication of the aging process

Equally intriguing were the age associated changes of resting tension With increasing age L_{max} was significantly shifted to the right and there was a significant increase in passive stiffness equivalent changes in muscle length brought about twice as much increase in resting tension in the older muscle as in the normal mature muscle It is apparent that the resistance to stretch changes during aging From the length at which resting tension was first detected normally mature muscles could be stretched by as much as 10 per cent before reaching L_{max} while the old muscles would only allow a 6 per cent stretch before reaching the same optimal length

Summary

The effects of aging on mechanical performance of isolated canine right ventricular trabeculae were studied in two age groups The first group was comprised of nine dogs about 9 months of age The second group was composed of seven dogs over 8 years of age Aging had no significant effect on developed force Extent of shortening tended to decrease There was a significant decrease in both the rate of rise of tension and the velocity of shortening (20 per cent) This reduction was primarily due to an increased duration of contraction Twitch duration increased by as much as 40 per cent during aging but most of this

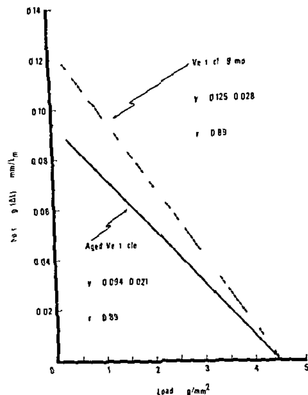


Fig 3 The extent of shortening at a load of 1 g was not significantly different at a $p < 0.05$ level between the young adult and the older muscles *(see Table II)* The y intercepts however were significantly different The two curves represent the linear regressions of all data points collected

prolongation was due to a profound slowing of relaxation Aging caused a significant increase in passive stiffness since equivalent changes in muscle length brought about twice as much increase in resting tension in the aged muscle as in the young muscle On the other hand aging caused a significant shift of L to the right Taken collectively these results indicate that aging is associated with increased passive stiffness and decreased speed of contraction without changes in strength

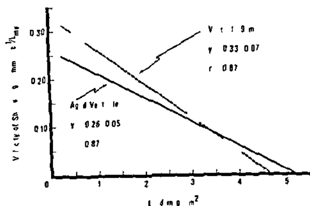


Fig 4 The velocity of shortening was significantly diminished in the old muscles

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The prevention and reversal of digoxin intoxication with specific antibodies

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Signs of intoxication may be expected to occur in 10 to 20 per cent of all digitalized patients[1, 7, 11, 1] Glycoside poisoning proves fatal in 5 to 10 per cent of all cases, the figure rising to 20 to 25 per cent when a massive overdose is taken notably with suicidal intent[3, 8, 1] At the present time treatment is limited to symptomatic measures which are not always satisfactory No effective antidote is as yet available

Animal experiments with digoxin specific antibodies[6, 9, 13, 14, 18] and the first successful use of Fab fragments with anti digoxin specificity in a case of attempted suicide[17] offer the prospect of a new form of causal therapy

The present paper is a report on the production of digoxin specific antibodies and the efficacy of various antibody fractions for the prevention and treatment of digoxin induced arrhythmias in cats

Methods

1 Production of antibodies Digoxin was oxidized with periodate and bound to human albumin[16] Yearling sheep were immunized with the digoxin-albumin conjugate in Freund's complete adjuvant and were given booster doses at intervals of 14 days On each occasion 3 mg of antigen was administered One month after the start of immunization, blood was sampled every 14 days The concentration of digoxin antibodies in the serum was determined spectrophotometrically after isolation with an immunoabsorbent prepared as previously described[6], it varied between 4 and 10 mg /ml

Digoxin specific sheep gammaglobulin was precipitated from anti digoxin antiserum by 40 per cent saturation with ammonium sulphate

The specific antibodies were isolated with the aid of an immuno absorbent consisting of ouabain-ribonuclease conjugate cross reacting with digoxin specific antibodies and coupled to Sepharose 4B[16] The antibodies were separated into two fractions on Sephadex G 200 (100 × 25 cm) One was a macroglobulin fraction (60 per cent) and the other was a fraction corresponding to 7 S gammaglobulin (40 per cent) (Fig 1) It was shown by immunoelectrophoresis using specific sera against sheep proteins (anti whole sheep anti sheep IgG and anti sheep IgM) that both fractions consisted of IgG The macroglobulin fraction was thus aggregated IgG

F (ab')2 was prepared by splitting the gamma globulin fraction with pepsin[10] isolation of F (ab)2 and intact IgG by immunoadsorption and separating off the intact IgG by fractionation on Sephadex G 200 (Fig 2)

2 Animal experiments Experiments were performed in spontaneously breathing adult cats of either sex with a body weight between 2 1 and 2 9 kilograms The cats were anesthetized with intra muscular doses of 43 mg /Kg chloralose and 430 mg /Kg urethan The trachea and a jugular vein were cannulated Heart rate and mean blood pressure were recorded continuously by means of a catheter in a femoral artery using a Statham P23Db transducer and a polygraph (Texas In

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Received for publication Dec 12 1977
Accepted for publication Jan 26 1978

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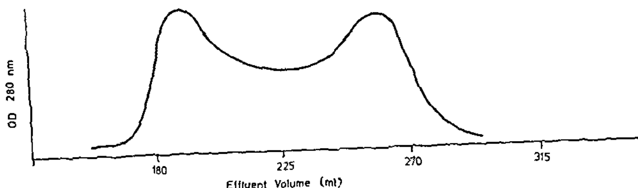


Fig 1 Filtration of isolated anti digoxin antibodies through Sephadex G 200 The first peak corresponds to the elution volume of macroglobulins and consists of aggregated IgG The second peak corresponds to the elution volume of 7 S (monomeric) IgG

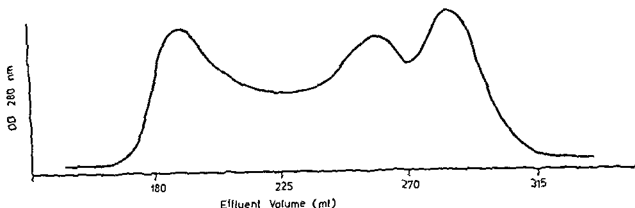


Fig 2 Filtration of pepsin treated anti digoxin antibodies through Sephadex G 200 The first and second peak consist of undigested IgG (Fig 1) the third peak consists of F(ab)2 fragments.

struments) The ECG (Leads I II and III 50 mm/sec) was taken with subcutaneous needle electrodes monitored on an oscilloscope and recorded on a 3 channel mingograph at intervals of 5 minutes and additionally whenever arrhythmias occurred

A Prophylactic administration of digoxin specific antibodies After the animals had been anesthetized digoxin was administered by infusion into a jugular vein at a rate of 10 μg/Kg/min The concentration of the infusion solution was matched to the individual body weight of each animal while the infusion volume was kept constant at 0.2 ml/min At the onset of ventricular tachycardia or when ventricular extrasystoles exceeded 50 per cent the infusion of digoxin was stopped and the survival time was measured

The effectiveness of three antibody preparations (gammaglobulin IgG and F (ab)2) was investigated by comparing the three groups of treated animals with an untreated control group

CONTROLS (Group 1 animals 1 to 5) The animals did not receive prophylactic treatment with digoxin specific antibodies

PROPHYLAXIS WITH DIGOXIN SPECIFIC ANTIBODIES (Groups 2 3 and 4) Immediately before administration of digoxin the animals received an intravenous infusion (10 to 20 ml 1 ml/min) of

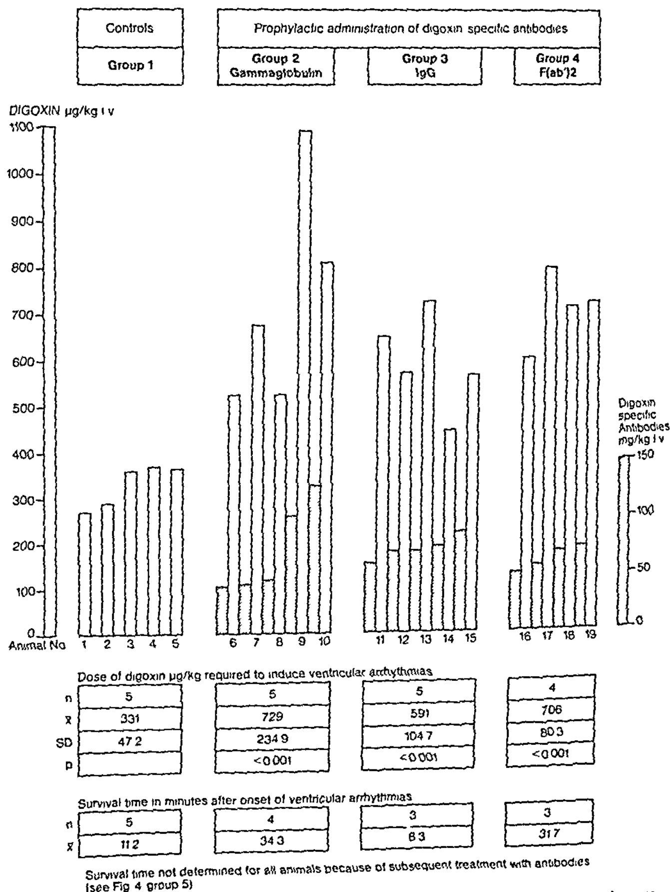
gammaglobulin (precipitated from anti digoxin antiserum with ammonium sulphate at 40 per cent saturation)

(Group 2 animals 6 to 10) The antibody doses varied between 42 and 129 mg/Kg

IgG anti digoxin antibodies

(Group 3 animals 11 to 15) The antibody doses varied between 62 and 88 mg/Kg Two animals (Nos 11 and 12) received the macroglobulin and the 7S fraction and 3 animals (Nos 13 14 15) only the 7S fraction

F (ab)2 fragment of digoxin specific antibody



	Group 1	Group 2	Group 3	Group 4
n	5	5	5	4
x̄	331	729	591	706
SD	47 2	234 9	104 7	80 3
p		<0 001	<0 001	<0 001

	Group 1	Group 2	Group 3	Group 4
n	5	4	3	3
x̄	11 2	34 3	6 3	31 7

Fig 3 Effects of prophylactic administration of digoxin specific antibodies in anesthetized cats Antibodies were injected intravenously before infusion of digoxin 10 µg/kg /min

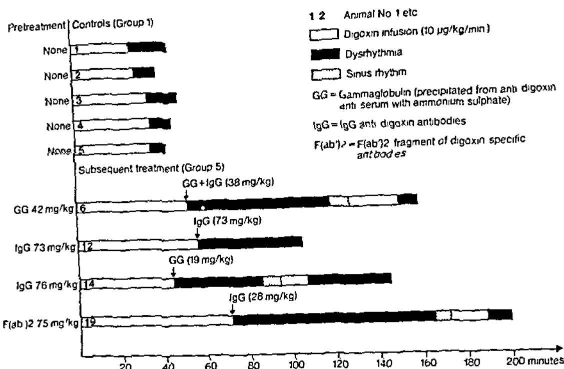


Fig 4 The influence of digoxin specific antibodies on digoxin induced arrhythmias in anesthetized cats Subsequent treatment with antibodies was performed in animals from which results are also presented in Fig 3 The time at the end of each column represents death of the cats

Table I Serum electrolytes before and after administration of the antibody preparations to 4 animals by infusion (*p* = not significant for all electrolytes)

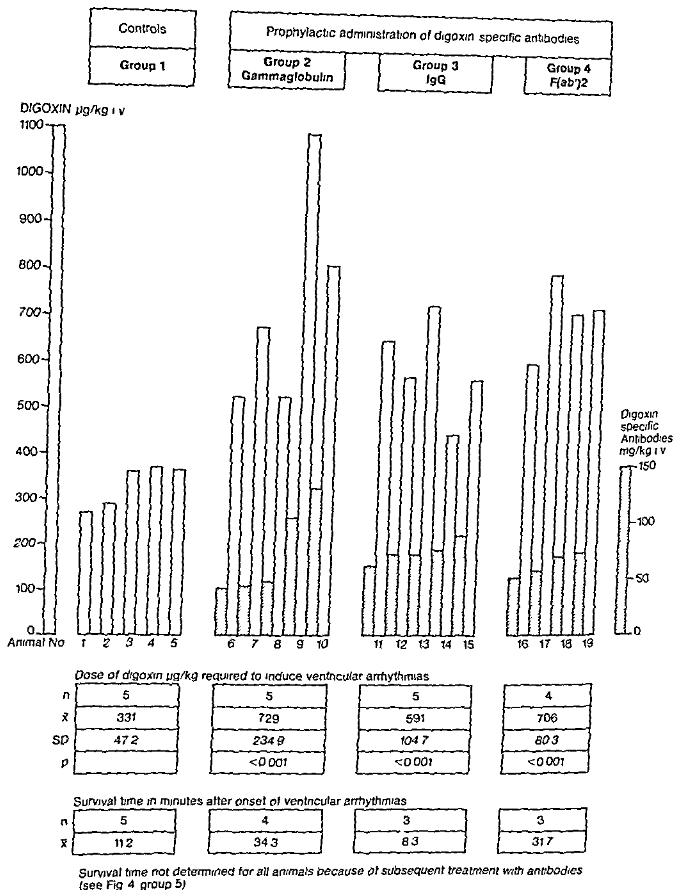
Animal no	Sodium (mmol/L)		Potassium (mmol/L)		Calcium (mg/100 ml)		Inorganic phosphorus (mg/100 ml)	
	Before	After	Before	After	Before	After	Before	After
13	147	149	3.77	3.67	9.4	8.2	4.35	4.16
17	152	153	4.05	3.70	9.0	8.8	4.87	4.47
18	148	147	3.45	3.40	10.1	9.45	5.00	4.76
19	149	145	3.41	3.24	9.5	8.5	4.46	4.09

(Group 4 animals 16 to 19) The antibody doses varied between 52 and 75 mg/kg

In four animals (Group 5 animals No 6 12 14 19) a treatment with digoxin specific antibodies after onset of the ventricular dysrhythmia was performed The antibody doses varied between 19 and 73 mg/kg

The serum levels of sodium potassium calcium and inorganic phosphorus were determined before and after infusion of the antibodies in four animals (Nos 13 17 18 19)

B Therapeutic administration of digoxin specific antibodies The animals were digitalized with daily intramuscular doses of 30 µg/Kg digoxin administered on 3 consecutive days and were observed for any side effects On day 4 the animals were anaesthetized and prepared as described above Digoxin was then administered via a catheter in the jugular vein at intervals of 15 minutes in a dose of 20 µg/Kg for the first two injections and in a dose of 10 µg/Kg for the third and subsequent injections until ventricular tachycardia developed If a normal sinus rhythm was not re established within 120 minutes the



Dose of digoxin µg/kg required to induce ventricular arrhythmias

	Group 1	Group 2	Group 3	Group 4
n	5	5	5	4
$\bar{x}$	331	729	591	706
SD	47 2	234 9	104 7	80 3
p		<0 001	<0 001	<0 001

Survival time in minutes after onset of ventricular arrhythmias

	Group 1	Group 2	Group 3	Group 4
n	5	4	3	3
$\bar{x}$	11 2	34 3	8 3	31 7

Survival time not determined for all animals because of subsequent treatment with antibodies (see Fig 4 group 5)

Fig 3 Effects of prophylactic administration of digoxin specific antibodies in anesthetized cats Antibodies were injected intravenously before infusion of digoxin 10 µg/Kg /min

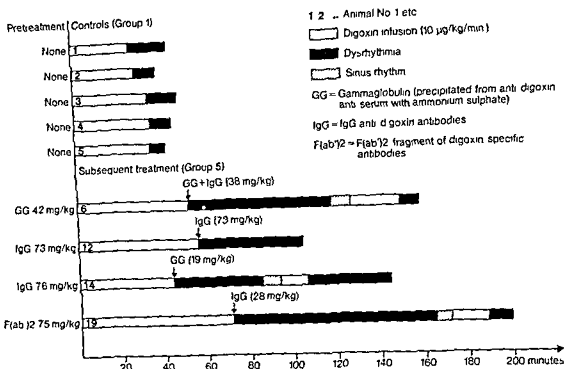


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Table I Serum electrolytes before and after administration of the antibody preparations to 4 animals by infusion (p = not significant for all electrolytes)

	Sodium (mmol /L)		*Potassium (mmol /L)*		*Calcium (mg /100 mL)*		*Inorganic phosphorus (mg /100 mL)*	
Animal no	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*
13	147	142	3 47	3 67	9 4	8 9	4 35	4 16
17	15[illegible]	15[illegible]	4 05	3 [illegible]0	9 0	8 8	4 87	4 47
18	148	147	3 45	3 40	10 1	9 45	5 00	4 76
19	149	145	3 41	3 24	9 5	8.5	4 46	4 09

(Group 4 animals 16 to 19) The antibody doses varied between 52 and 75 mg /Kg

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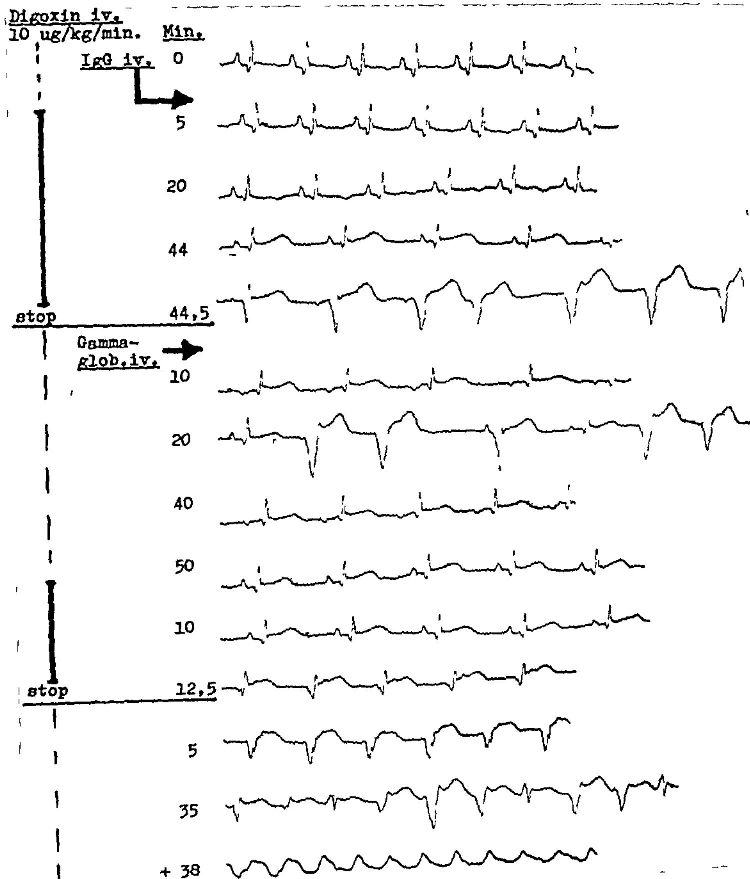


Fig 5 *ECG (Lead II 50 mm /sec) of animal No 14* Prophylactic treatment with IgG (76 mg /Kg) Forty four minutes after the start of the digoxin infusion sinus bradycardia and S T changes after 44 5 minutes (= 445 µg/Kg digoxin) onset of ventricular tachycardia Intravenous treatment with gammaglobulin (19 mg /Kg) Ten minutes later nodal rhythm occurred after 50 minutes stable sinus rhythm resumed On renewed infusion of digoxin arrhythmia again induced after 12 5 minutes (= 125 µg/Kg digoxin) with the resulting death of the animal

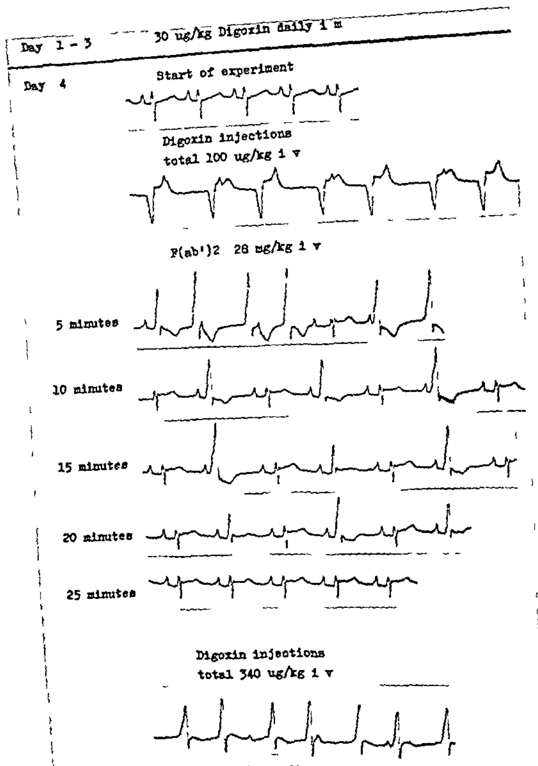


Fig 8 *ECG (Lead III 50 mm./sec) of animal No 26* Daily intramuscular doses of digoxin (30 μg/Kg) on day 1 to 3. On day 4 after injection of total 100 μg/Kg digoxin ventricular tachycardia appeared Intravenous treatment with F(ab')2 28 mg/Kg was initiated 25 minutes later stable sinus rhythm resumed. To induce renewed ventricular dysrhythmia, total injections of 340 μg/Kg digoxin were needed.

Table II Therapeutic administration of digoxin specific antibodies

Digitalization with digoxin 30 µg/Kg daily for 3 consecutive days	Side effects	Rhythm at the start of experiment	Dose of digoxin (µg/Kg) needed to trigger ventricular tachycardia		F(ab')2 (mg/kg) iv
Controls (Group 6)					
Animal 20	None	Sinus	90		–
Animal 21	None	Sinus	70		–
Animal 22	None	Sinus	80	$\bar{x}$ = 78	–
Animal 23	Loss of weight	Sinus	70	SD = 8 4	–
Animal 24	Loss of weight vomiting	Sinus	80		–
				p < 0 3	
Treatment F(ab')2 (Group 7)					
Animal 25	Loss of weight vomiting	Sinus	50		24
Animal 26	None	Sinus	100		28
Animal 27	None	Sinus	70	$\bar{x}$ = 70	29
Animal 28	Vomiting	Sinus	60	SD = 17 9	31
Animal 29	Loss of weight	Sinus	80		35
Animal 30	Loss of weight	Sinus	60		64
Day 1 3					Day 4

animals were killed When the ventricular tachycardia converted within this time to a stable sinus rhythm which was uninterrupted for at least 10 minutes by signs of arrhythmia, the dose of digoxin required to induce renewed ventricular tachycardia was determined Digoxin was administered intravenously at intervals of 5 minutes in a dose of 20 µg/Kg for the first 7 injections and in a dose of 40 µg/Kg for the eighth and subsequent injections

Two groups of animals were investigated (1) *Controls* (Group 6 animals 20 to 24) These animals did not receive any treatment after induction of ventricular tachycardia (2) *F (ab')2 treatment* (Group 7, animals 25 to 30) After onset of ventricular tachycardia F (ab')2 fragment of digoxin specific antibodies was administered intravenously in a dose of 28 to 64 mg/Kg

The results were tested for significance by Student s t test

Results

A Prophylactic administration of digoxin specific antibodies (Fig 3)

Controls (Group 1, animals 1 to 5) 270 to 370 (x = 331, SD = 47) µg/Kg digoxin were needed to induce ventricular dysrhythmia The survival time after discontinuing the digoxin infusion was 6 5 to 18 (mean 11 2) minutes

Prophylaxis with digoxin specific antibodies (Group 2 3 and 4) The dose of digoxin required to induce dysrhythmia was significantly ($p < 0\ 001$) greater for all prophylactically treated groups than for the control group The digoxin doses were as follows (1) gammaglobulin from anti digoxin antiserum (Group 2 animals 6 to 10) 525 to 1085 ($\bar{x}$ = 729, SD = 235) µg/Kg digoxin, (2) IgG anti digoxin antibodies (Group 3, animals 11 to 15) 445 to 725 ($\bar{x}$ = 591, SD = 105) µg/Kg digoxin, (3) F (ab')2 fragment of the digoxin specific antibodies (Group 4, animals 16 to 19) 600 to 795 ($\bar{x}$ = 591 SD = 80) µg/Kg digoxin

The mean survival time for the animals in group 2 (34 3 minutes) and Group 4 (31 7 minutes) was significantly ($p < 0\ 02$) longer than for the control animals whereas the survival time for Group 3 (mean 8 3 minutes) did not differ from that for the control group

Serum levels of sodium potassium calcium and inorganic phosphorus measured in four animals were not significantly affected by infusion of the antibody preparation (Table I)

Course	*Dose of digoxin (μg/Kg) required to re-induce ventricular tachycardia*
Died 45 min after onset of ventricular tachycardia	–
Died 56 min after onset of ventricular tachycardia	–
Died 89 min after onset of ventricular tachycardia	–
Ventricular tachycardia still persisted after 120 min (killed)	–
Ventricular tachycardia still persisted after 120 min (killed)	–
Stable sinus rhythm after 95 min	280
Stable sinus rhythm after 25 min	340
Stable sinus rhythm after 31 min	300
Stable sinus rhythm after 30 min	220
Stable sinus rhythm after 27 min	420
Stable sinus rhythm after 57 min	600

Of the four prophylactically treated animals which again received digoxin specific antibodies (gammaglobulin or IgG) after onset of the ventricular dysrhythmia three survived and were in stable sinus rhythm 50 to 100 (on average 75) minutes later (Figs 4 and 5) Between 125 and 220 (on average 168) μg/Kg digoxin was required to re-induce ventricular dysrhythmia in these animals and they survived the second arrhythmia for an average period of 19 minutes One animal died after 48 minutes despite the subsequent treatment and without conversion to sinus rhythm

B Therapeutic administration of digoxin specific antibodies (Table II) No difference was observed between the control animals (Group 6 animals 20 to 24) and the animals treated with F (ab)2 (Group 7 animals 25 to 30) after digitalization over 3 days with digoxin a few animals in both groups suffered from vomiting and loss of weight After anaesthetization and preparation all were in sinus rhythm There was no significant difference between the doses of digoxin required to induce ventricular tachycardia in the two groups

Conversion to stable sinus rhythm did not occur in *any* of the controls Three animals died 45 56 and 89 minutes after onset of ventricular tachycardia two animals were still dysrhythmic after 120 minutes and were killed

Stable sinus rhythm was reinstated in all the animals treated with *F (ab)2 fragment of digoxin specific antibodies* Conversion to sinus rhythm occurred after a minimum time of 25 minutes and a maximum time of 95 minutes (mean time 43 minutes) Prior to conversion moreover short periods of sinus rhythm were observed which again passed into phases of ventricular tachycardia or ventricular extrasystoles (Fig 6)

Digoxin doses of 220 to 600 (mean 360) μg/Kg were needed in order to induce ventricular tachycardia again after reinstatement of stable sinus rhythm in the animals treated with antibodies and a relation between digoxin dose and dose of antibody administered was discernible

Discussion

In 1966 Butler and Chen[1] described the preparation of heterologous digoxin specific antibodies Butler and co-workers subsequently demonstrated the effectiveness of the antibodies for prevention and reversal of the effect of the glycoside in vitro [9, 16] and in animal experiments especially in digoxin intoxication [8, 12, 2] The Fab fragment of sheep digoxin specific antibodies was first successfully employed in a human subject with potentially lethal digoxin poisoning in 1976[17] As far as we are aware no other patients have so far been treated

The frequency of glycoside intoxication and the considerable mortality rate prompted these present investigations with digoxin specific antibodies with a view to their clinical use

Used prophylactically the digoxin specific antibodies in the form of preparations of gammaglobulin IgG or F (ab)2 had a statistically significant protective effect in our experiments on anaesthetized cats Depending upon the dose of antibody administered the dose of digoxin required to induce ventricular dysrhythmia was up to three times greater than in untreated control animals The arrhythmia induced by the glycoside led to the death of all the animals from ventricular fibrillation and asystole For this reason four animals were given additional digoxin specific antibodies in the form of gammaglobulin or IgG after onset of the digitalis induced arrhythmia

One of these subsequently treated animals died despite a high dose of antibodies and did not revert to sinus rhythm However, this particular animal had shown transient ventricular fibrilla tion shortly after onset of the digoxin induced ventricular tachycardia The remaining three animals were again in stable sinus rhythm 50 to 100 minutes later, and sinus rhythm was frequently restored for short periods even earlier than this

Digoxin specific antibodies were found to be highly effective in the treatment of digoxin induced arrhythmia Five untreated controls were digitalized over 3 days and on the fourth day ventricular tachycardia was induced with injec tions of digoxin Of these five animals, three died early and the other two were still in ventricular tachycardia after 120 minutes By contrast stable sinus rhythm was re established in all six animals treated with F (ab)2 after an average time of 43 minutes In similar experiments in dogs with the Fab fragment of digoxin specific antibodies conversion to sinus rhythm was achieved as early as 20 minutes after administration [6] The different times taken may be due to the different experi mental procedure or to the fact that F (ab)2 is distributed more slowly through the compart ments than Fab

It proved possible in all the animals treated with specific antibodies to induce renewed toxic arrhythmias with digoxin This is evidence that the cardiac glycoside receptors of the myocar dium are not blocked by pharmacologically inac tive antibody hapten complexes Investigations on the isolated papillary muscle of the cat[4] lend support to such a view

Pharmacokinetic studies in the dog suggest that the Fab fragment of digoxin specific anti bodies probably has considerable advantages over the intact antibodies the smaller size of the molecule permits more rapid distribution and diffusion in the extravasal compartment and more rapid renal excretion of the digox in-Fab-complex by glomerular filtration Fab and F (ab)2 have a shorter half life in the orga nism than the intact immunoglobulin molecules and since they lack the Fc component they probably have a lower immunogenicity than the intact molecules Our antibody preparations were in general well tolerated in these acute experiments as judged from the heart rate blood pressure respiration, and ECG The risk of sensi tization to foreign protein is at present an obstacle to the wider clinical use of digoxin specific antibodies At the present time such treatment should be reserved for cases in which conventional treatment is without avail and which are likely to prove fatal

Summary

The formation of digoxin specific antibodies was induced in sheep by immunization with a digoxin-albumin conjugate The efficacy of the antibodies was investigated in anesthetized cats

When the digoxin specific antibodies were administered prophylactically as a gammaglobu lin IgG or F (ab)2 preparation the dose of digoxin needed to induce ventricular dysrhythmia was significantly greater ($p < 0.001$) for the pretreated animals than for the controls

To investigate therapeutic efficacy the animals were digitalized with digoxin over a period of three days and were given digoxin injections on the fourth day to provoke ventricular tachycar dia Of the control animals three died before two hours had elapsed and the arrhythmia persisted in the two remaining animals By contrast a stable sinus rhythm was restored in all animals which were treated with F (ab)2 fragment of the digoxin specific antibodies after onset of ventric ular tachycardia The doses of digoxin required to trigger renewed ventricular dysrhythmia in these animals were greater than those required at the start of the experiment

The potential clinical use of digoxin specific antibodies is discussed in the light of these results and reports in the literature

We are grateful to *Miss Ischi and Miss Dosogne* for their technical assistance and to Mr J E Smith for his English translation of the manuscript

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Transmural gradients of experimental myocardial ischemia Limited correlation of ultrastructure with epicardial S-T segment elevation

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Relatively short periods of experimentally induced ischemia produce functional, electrocardiographic, and morphologic changes in the working canine heart [1] Maroko and associates [3] have presented evidence that the height of epicardial S T segment elevation in the ischemic canine heart may be a useful indicator of both the extent and the severity of underlying myocardial injury, and that epicardial S T segment elevations recorded after 15 minutes of permanent coronary occlusion correlate well with changes in myocardial morphology at 24 hours [4] with myocardial creatine phosphokinase depletion,[2, 3] and with regional myocardial blood flow [5] The practical value of such observations has been challenged [6, 8] for definite inconsistencies have been observed For example other investigators have not found close correlation between the extent of myocardial injury and the height of S T segment elevation [9] and functional changes in the myocardium have been shown to persist long after S T segments have reverted to normal [1?]

In view of these conflicting data we undertook a series of experiments designed to explore the transmural ultrastructural state of the myocardium immediately underlying sites of epicardial S T segment recording in the canine heart Several investigators have asserted that ischemic injury resulting from coronary occlusion of twenty minutes or less is completely reversible [11, 13] In two of these reports [11, 1] morphologic alterations were observed after temporary circumflex coronary artery occlusion They describe the pathologic findings in the posterior papillary muscle of the dog The commonly used technique of epicardial S T segment mapping describes changes in the myocardium of the antero apical left ventricle of the dog [2] By means of standardized fixation and sampling techniques, we were able to characterize reproducible gradients of ischemic morphologic change across the anterior apical ventricular wall and to correlate these with simultaneously recorded epicardial electrocardiograms In this report we present data dealing with the effects of 20 minutes of ischemia

Materials and methods

Our objective was to obtain epicardial electrocardiographic recordings over ischemic and non ischemic zones of myocardium and to study the ultrastructure of transmural samples of myocardium immediately beneath any selected recording point To this end we utilized a technique for rapid perfusion fixation of the entire heart immediately after recording the electrophysiologic changes This procedure provided a rigid and

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Supported by the Louis L Block Fund of The University of Chicago Grant HL17648 awarded by The National Heart Lung and Blood Institute DHEW and American Heart Association Grant 76 632

Received for publication Jan 16 1978

Accepted for publication Feb 13 1978

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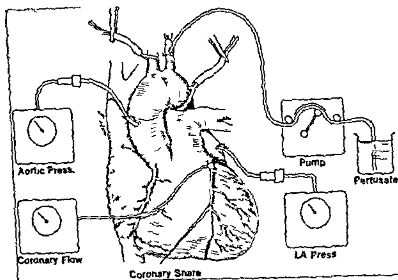


Fig 1 Schematic diagram of experimental preparation for immediate perfusion-fixation of the heart in situ

uniformly fixed specimen suitable for precise sampling. Ventricles were in a nearly diastolic configuration [5] and anatomic landmarks were well preserved permitting points of recording and zones of grossly observed ischemia to be marked accurately on the epicardial surface

Operative procedures Mongrel dogs weighing between 15 and 40 kilograms were anesthetized with sodium pentobarbital intubated and ventilated with a Harvard respirator * Arterial blood gases were determined and supplemental oxygen was utilized as necessary to maintain the arterial PO at normal levels. In each instance the heart was exposed through a left thoracotomy incision and suspended in a pericardial cradle An electromagnetic flow probe† was placed around the left anterior descending coronary artery (LAD) at its origin and pressure monitoring catheters were placed in the ascending aorta and in the right and left atria Arterial and atrial pressures were measured with Statham pressure transducers ‡ The right brachiocephalic trunk was ligated and cannulated proximal to the ligature with a large bore tube for subsequent perfusion fixation The descending aorta distal to the ligamentum arteriosum was encircled with a snare The mid portion of the left anterior descending coronary artery (LAD) or one of its major branches was selected for occlusion dissected free of epicardial adipose tissue and encircled with an atraumatic silicone rubber tape Occlusion sites were selected after evaluation of coronary artery distribution with the aim of producing a zone of ischemia involving the distal antero lateral or antero apical portion of the left ventricle After recording baseline hemodynamic data and determining hematocrit and serum osmolarity the coronary artery was occluded for a period of 20 minutes

A saline soaked wick connected to the V lead of an ECG amplifier was used to record the epicardial electrocardiogram from selected epicardial sites [2] All variables including epicardial and limb electrocardiograms were monitored and recorded on an Electronics for Medicine recorder At five minute intervals epicardial electrocardiograms were recorded at eight to 12 sites along the distribution of the LAD [2] After 20 minutes the heart was fibrillated by means of low voltage direct current the coronary ligature was released and perfusion fixation began immediately

Perfusion-Fixation Coronary perfusion was achieved by closing the snares around the brachiocephalic trunk and the descending aorta opening the left and right atria to vent the heart and starting a calibrated roller pump which propelled fluid into the brachiocephalic cannula (Fig 1) Fibrillation prior to snare occlusion prevented acute left ventricular afterload in

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crease and allowed immediate coronary perfusion The coronary arteries were first perfused with balanced electrolyte solution, until the coronary sinus effluent was grossly clear of blood, this usually was achieved in one to two minutes The perfusate was then changed to 2 per cent glutaraldehyde solution, and perfusion continued The fixative solution was prepared by diluting concentrated glutaraldehyde solution (50 per cent) with distilled water, adjusting the pH to 7 4 with sodium hydroxide, and adding sodium chloride to adjust the osmolality to the appropriate level for the animal under study Serum osmolality of the animals studied ranged from 297 to 316 mosm The osmolalities of the balanced electrolyte and 2 per cent glutaraldehyde solutions used for perfusion were corrected to within 2 per cent of the serum osmolality of each dog studied prior to perfusion Both the flushing and fixation solutions were maintained at 37° C in a water bath Pressure in the ascending aorta was monitored throughout perfusion, and pump speed was adjusted to maintain perfusion pressure at a mean level of 90 mm Hg Overflow of fixative from the atrial vents accumulated in the pericardial well and prevented drying of the epicardial surface during the fixation period Hearts were completely fixed, with excellent preservation of ultrastructural detail *after 30 minutes of* controlled pressure perfusion at 37° C

Specimen sampling and preparation At the conclusion of the perfusion-fixation period, the heart was removed from the thorax by transsection of the major vessels and immersed in a container of fixative The sites of S T segment mapping were marked on the epicardium with indelible ink, according to maps drawn at the time of recording, and the specimen was photographed Ischemic zone sampling sites were selected on the basis of anatomic location, appearance during coronary occlusion, and S T segment elevation Regions distant from zones of presumed ischemia and with isoelectric S T segments were sampled as non ischemic, normal controls for each heart Large transmural tissue blocks were *removed from ischemic and non* ischemic zones by means of a sharp flat sectioning knife Each tissue block measured approximately 1 0 × 1 0 cm at the endocardial and epicardial surfaces Final sampling was accomplished by subdividing each block under a dissecting microscope Cuts were made perpendicular to the epicardial surface to produce a column of tissue approximately 1 5 mm on each edge and of a length determined by the thickness of the ventricle Thus, each column had the ink dot marked epicardium at one end and the corresponding endocardium at the other One of the trimmings facing the final column sample was processed for study by light microscopy The column was then divided into 1 0 to 2 0 mm cubes, each of which was placed in a separate vial and numbered consecutively from epicardium to endocardium Eight to 15 transventricular samples were therefore available at each site, depending upon ventricular thickness Each transmural cube was post fixed in 1 per cent osmium tetroxide for one hour, dehydrated in graded alcohol solutions and propylene oxide, and embedded in epon

Subepicardial subendocardial, and midventricular specimens were sectioned *from each* sampling location Selected specimens at other levels were viewed in some instances to confirm the presence of transmural gradients Thick sections were stained with toluidine blue For thin sectioning specimens were reoriented when necessary to provide longitudinal sections of myocardial fibers Thin sections were treated with lead hydroxide and uranyl acetate to enhance electron density and were viewed in an RCA EMU 3D electron microscope In each heart a section from the non ischemic zone was compared to at least one sample from the ischemic zone In some hearts two sites in the ischemic zone were analyzed to allow comparison of ischemic sites with differing degrees of S T segment elevation Sections were examined and photographed systematically at a standard series of magnifications in order to obtain comparable data with regard to nuclear morphology, abundance of glycogen mitochondrial preservation, and the state of sarcomeres filaments membranes, and intercalated discs Perfusion fixed specimens tended to show larger intra and extra cellular spaces than are normally seen after immersion fixation but comparison of samples from ischemic and non ischemic zones permitted evaluation of swelling due to ischemia Care was taken to observe and to photograph capillary endothelial cells and tissue histiocytes as often as possible in order to reveal non specific changes



Fig 2 Range of mitochondrial change associated with increasing severity of ischemic injury after 20 minutes of coronary occlusion. *A* In control zones with normal S T segments mitochondria are intact cristae are closely packed and uniformly oriented *B* In zones of moderate ischemic damage (+ +) mitochondria show focal intracristal widening *(arrows)* C In zones of severe ischemia (+ + + +) swollen mitochondria with foci of total cristal disruption are frequent (All magnifications originally ×44 000)

and to assess changes peculiar to myofiber ischemia Photographs were reviewed and compared as unknowns by each of the authors Analysis of the photographs revealed that ultrastructural changes could be graded in five steps (0 to 4+) When no ischemic alterations were found in any photographs of an individual myocardial sample the tissue was graded zero (0) Samples which revealed minimal clumping of nuclear chromatin patchy but definite decrease in glycogen stores and early alterations in mitochondrial structure were graded + Samples with mitochondrial disruption marked edema marked nuclear clumping and/or derangement of nuclear structure and severe depletion or absence of glycogen stores were graded + + + + Intermediate degrees of change were graded + + or + + +

Experiments The findings which form the basis of this report are drawn from 12 experiments In six fixation was carried out immediately after 20 minutes of coronary occlusion with epicardial mapping at five minute intervals In a second group of six animals the coronary artery snare was released after 20 minutes and additional epicardial electrocardiograms recorded five 15 30 and 60 minutes after reperfusion These experiments were then terminated by fibrillation and immediate perfusion-fixation

Results

Morphologic changes related to ischemic injury were similar to those reported by others [11, 12] Clumping and margination of nuclear chromatin were a striking and consistent finding when present this change was usually uniform in degree throughout the section and involved practically every myofiber nucleus Glycogen granule depletion was also a consistent finding but was much less uniform in any given block than was the nuclear change Mitochondrial change after 20 minutes of ischemia ranged from focal widening of intercristal spaces to over all mitochondrial swelling and focal disruption of cristal architecture For any given section mitochondrial changes were more uniform in extent and degree than glycogen depletion changes and less uniform than the nuclear changes Thus although mitochondrial changes paralleled nuclear changes these alterations could not always be shown side by side on photographs of the same magnification The sequence of severity of mitochondrial change is shown in Fig 2 The corresponding effects of ischemia on nuclear configura

Table I Transmural ultrastructure after 20 minutes of coronary occlusion

Dog	Epicardial electrocardiogram at 15 min		Sampling sites	Height of ST at 15 min (mm)	Myocardial thickness (mm)	Ultrastructural evidence of myocardial ischemia		
	N ST > 2	Σ ST				Subendocardial	Midmyocardial	Subepicardial
A	0	0	NI	0 0	11	0	0	0
			I	0 0	11	++++	0	0
B	0	5	NI	0 0	20	+	0	0
			I_1	1 0	15	++	++	0
			I_2	2 0	15	++++	+++	+
C	4	26	NI	2 0	20	0	0	0
			I_1	2 0	16	++	+++	0
			I_2	6 0	12	+++	++	+
D	6	35	NI	1 5	12	0	0	0
			I	5 0	10	++	+	0
E	5	41	NI	0 0	20	0	0	0
			I	7 0	18	+++	++	+
F	7	85	NI	1 0	14	0	0	0
			I	4 0	12	++++	++	+
			I_2	13 0	11	+++	++	0

+ = no ischemic change + to ++++ = increasing ultrastructural evidence of ischemia (See text) NI = non ischemic zone by anatomic criteria and gross appearance before fixation I I = ischemic zone by anatomic criteria and gross appearance before fixation

tion and glycogen granules are better seen at the lower magnifications used in subsequent illustrations Except for Fig 2 all illustrations are presented at the same magnifications to permit ready comparison, fields have been chosen to represent typical composite findings

In no instances were the ischemic changes so consistently evident in myocardial fibers, seen in capillary endothelial cells, tissue histiocytes, or fibroblasts even when these interstitial cells were immediately adjacent to abnormal myofibers We interpreted this finding to be a reflection of the differential effects of ischemia on these cells and as further evidence that the changes we noted were not attributable to inadequate penetration of fixative Specimens from control areas i e away from presumed ischemic zones and without S T segment elevation showed good preservation of myocardium at all depths

Correlations Between S T segment elevation and ultrastructural change after 20 minutes of ischemia The results for the six dogs studied immediately after 20 minutes of LAD occlusion are presented in Table I *in order of increasing* S T segment change The number of sites of S T segment elevation greater than 2 mm (N ST) and the sum of S T elevation (Σ ST) at 15 minutes of ischemia are presented in a manner similar to that used by others describing comparable experiments[2] Thickness of myocardium height of epicardial S T segments at sampling sites and the state of the myocardium at typical depths of sampling are given for each site The number of sites of ST (N ST) segment elevation greater than 2 mm ranged from 0 to 7 ($\overline{4}$) The sum of S T segment elevation (Σ ST) in the ischemic areas ranged from 0 to 85 mm ($\overline{32}$) Except for the animal with no S T segment elevation (Dog A) abnormal areas of myocardium were grossly visible after occlusion of the coronary branch In most instances, there was cyanosis of the myocardium distal to the ligature with paradoxical bulging during systole A gradient of increasing ischemic ultrastructural change from epicardium to endocardium was seen in all the ischemic zone samples Samples from non ischemic zones appeared normal in all cases except the subendocardial sample in Dog B, where minimal alterations in nuclear chromatin and mitochondria were noted The ischemic zone sample sites in animal B, however followed the consistent pattern of transmural gradient of change seen in the other five animals studied at 20 minutes

S T segment elevations in ischemic zones were always associated with underlying morphologic evidence of injury but there was not a consistent

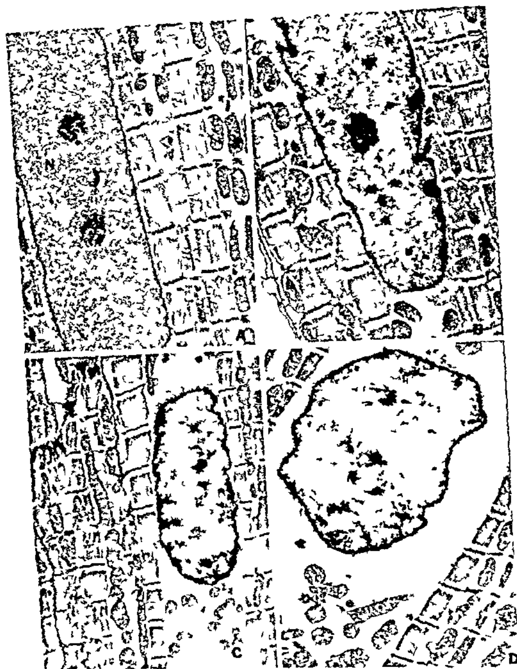


Fig. 3. Typical fields from myocardial samples after twenty minutes of coronary occlusion in a single animal (Dog F). A transmural gradient of injury from epicardium to endocardium underlies the abnormal S-T segment elevation of 4 mm. *A*, Subendocardial zone from control area, i.e., away from zone of ischemia and underlying a normal S-T segment. Nucleus (N) and mitochondria (m) are intact and glycogen (*g*) is abundant. *B*, subepicardial sample (Site I) underlying abnormal S-T segment. Nuclear chromatin clumping and margination is moderate, glycogen is depleted, and mitochondria show focal intercristal swelling and blebbing. *C*, Midmyocardial sample (Site I) (0.8 cm. from epicardial surface). Nuclear chromatin clumping and margination are marked, glycogen is absent, and mitochondria show increased swelling and deformation. *D*, Subendocardial sample (Site I) (1.2 cm. from epicardial surface). Nucleus is practically translucent, glycogen is markedly depleted, and mitochondria are frequently disrupted. In addition, myofibers are thinned and attenuated with focal filament disruption. (All original magnifications × ,800.)

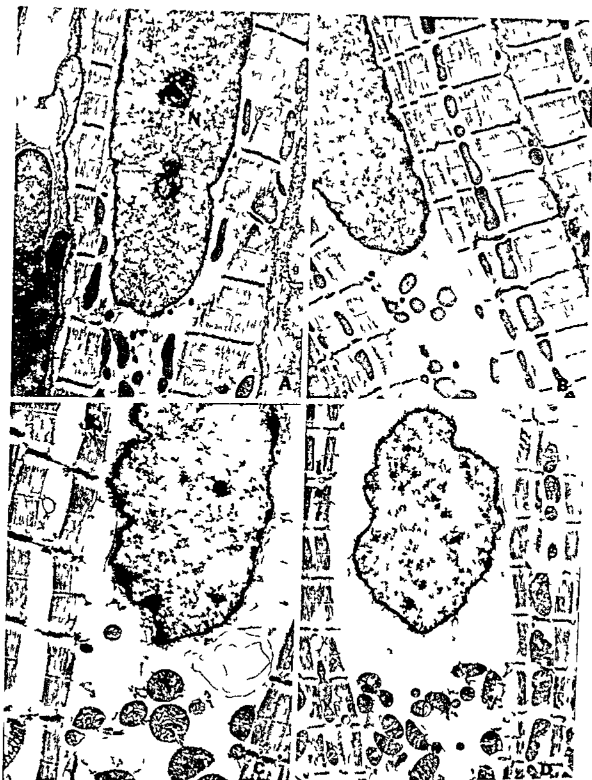


Fig 4 Specimen taken from an ischemic zone (Dog C) with minimal S T segment elevation (2 mm) In contrast to the findings in Fig 3 this zone showed no ischemic injury in the subepicardial sample ischemic damage was however evident in the midmyocardium and in the subendocardial sample *A* Subendocardial zone of control area Nucleus mitochondria and glycogen stores are normal *B* Subepicardial sample from the ischemic zone showed no abnormalities *C* Mid myocardial sample in the ischemic zone (0 8 cm from epicardial surface) Nuclear chromatin is clumped mitochondria are swollen glycogen is absent myofibers are attenuated *D* Subendocardial sample from ischemic zone (1 6 cm below epicardial surface) Mitochondrial damage is more severe edema is more pronounced nuclear chromatin is distinctly clumped and marginated glycogen is depleted (All original magnifications ×7 800)



Fig 5 Samples underlying a point in the ischemic zone with no elevation of S T segment (Dog A) Severe ischemic changes were present in the subendocardial sample *(B)* 1 7 cm below the epicardial surface There were only minimal ischemic changes in the midmyocardial sample *(A)* 0 9 cm below the surface There were no abnormalities in the subepicardial sample (All original magnifications ×7 800)

relationship between the extent of change and the height of S T segment elevation In addition zero or minimal elevation of S T segments could be associated with marked ischemic change Comparison of animals D and E for example would suggest a relationship between S T segment elevation and transmural extent of ischemic change In animal D an S T segment elevation of 5 mm was observed at the ischemic sampling site at this point the subepicardial myocardium was normal and identical to the non ischemic site while the subendocardial site 0 8 cm beneath the surface of the heart showed moderately advanced ischemic changes (+ +) and the mid myocardial sample revealed minimal change In animal E with a slightly higher S T segment elevation (i e., 7 mm) over the ischemic zone sample site morphologic abnormalities were present at all depths with a gradient of severity from epicardium to endocardium Other comparisons among ischemic zones even in blocks from different sites in the ischemic zone of the same animal failed to show a quantitative relationship between morphologic change and S T segment elevation Dog F for example showed the usual gradient of change from epicardium to endocardium in both of the samples ischemic zones one site (I_1) had more damage in the subendocardial layer than did the other site (I_2) but the latter had a higher S T segment elevation Typical fields from the non ischemic zone and from the subepicardial mid myocardial and subendocardial myocardium in ischemic zone I_1 of dog F are shown in Fig 3

In contrast minimal S T segment elevations could be associated with severe ischemic changes (Fig 4) In dog C two sites were studied in the ischemic zone One site showed a 2 mm S T segment elevation an elevation generally considered to be insignificant[2] In this area the subepicardial myocardium was intact but both the mid and the subendocardial samples showed marked ischemic changes Similarly the heart of the Dog A showed no S T segment elevations at a point expected to be ischemic on the basis of the anatomic site of vessel occlusion and the gross appearance of the myocardium during occlusion At this site moderate ischemic changes were seen

in the mid myocardium and marked abnormalities were seen in the subendocardial myocardium (Fig 5) The non ischemic, control zone in this animal was entirely normal Finally, dog B had minimal S T segment elevation at the sampled sites in the ischemic zone, although the myocardium appeared to be abnormal during coronary artery occlusion Significant ultrastructural abnormalities were prominent in both sample sites with the typical transmural gradient of severity

Reperfusion after 20 minutes of ischemia The six animals allowed to recover for 60 minutes after the ischemic interval had N ST ranging from 3 to 7 ($\overline{5}$), and Σ ST ranging from 27 5 to 62 mm ($\overline{44}$) 15 minutes after occlusion After release to the occlusion, the epicardial electrocardiogram returned to the control state in all animals before they were killed Myocardium in non ischemic zones appeared entirely normal Only slight and focal clumping of nuclear chromatin could be discerned in some subendocardial sites in the ischemic zone These nuclear changes were in marked contrast to the nearly universal changes observed after 20 minutes of ischemia in the other six dogs

Correlations with hemodynamic data Preligation heart rates ranged from 120 to 150 beats per minute while post ligation heart rates ranged from 120 to 180 beats per minute Tachycardia induced by myocardial ischemia did not correlate with either the extent or the degree of ultrastructural change in the samples examined Left atrial pressures ranged from 6 to 8 mm Hg and remained constant or rose slightly (1 to 2 mm Hg) after coronary ligation Hematocrit values ranged from 31 to 42 per cent and did not correlate with the extent or degree of ischemic damage Proximal LAD blood flow was reduced from 25 to 60 per cent during ligation of the distal LAD or its diagonal branch Animal F had the greatest decrease in LAD flow and correspondingly exhibited the most severe ischemic changes other animals showed no consistent relationship between the extent of proximal LAD flow decrease and the extent of morphologic alteration Mean arterial pressure ranged from 80 to 120 mm Hg in the six animals (A F) studied immediately after 20 minutes of ischemia and the extent of ischemic alteration did not correlate with the level of arterial pressure The six animals which underwent reperfusion and recovery after 20 minutes of ischemia had heart rates ranging from 120 to 180 beats per minute, mean arterial pressure ranging from 100 to 130 mm Hg and decreased coronary flow ranging from 35 per cent to 40 per cent

Discussion

In the present study our goal was to determine the transmural myocardial ultrastructural alterations which correspond to various degrees of S T segment elevation under conditions of reversible injury Controlled pressure perfusion-fixation of the arrested heart produced a uniformly fixed rigid specimen in which the myocardium could be sampled from epicardium to endocardium in precise relationship to S T segment recording sites Non ischemic zones were consistently normal in appearance from epicardium to endocardium, but, 20 minutes of coronary occlusion provided a distinct gradient of unequivocal injury in the ischemic zones Changes typical of ischemia were greatest as expected in the subendocardial region The most severe changes, graded + + + +, appeared to be somewhat more severe in the samples examined than those reported by others at 20 minutes of papillary muscle ischemia [1] Since animals which were allowed to recover before fixation exhibited no ultrastructural alterations in the previously ischemic zones we may presume that the observed ischemic changes were reversible

Despite care exercised in mapping fixation, and sampling in these experiments we were unable to demonstrate a consistent relationship between S T segment elevation and transmural morphologic changes We were thus unable to establish any quantitative or predictive value of epicardial S T segment mapping for determining the severity of the transmural, ultrastructural myocardial injury Although S T segment elevation in the anatomically ischemic zones always indicated the presence of ultrastructural changes marked changes in myocardial ultrastructure were also seen in ischemic zones when S T segment elevations were minimal In this model S T segment changes tend to underestimate the extent of early ischemic damage Heng and colleagues[9] also found that myocardial injury could be present at sites where S T segments were not elevated during early ischemia confirming our findings

There is other evidence to suggest that changes

in the epicardial electrocardiogram do not always predict changes in underlying myocardium Cohen and Kirk[7] found that apparent improvement in S-T segment elevation could be associated with increasing ischemia In another study comparing the effects of various methods of hemodilution on the acutely ischemic working heart significant reduction in S-T segment elevation was observed after dextran hemodilution but analysis of regional myocardial blood flow showed no change in ischemic zone blood flow when improvement in the epicardial electrocardiogram was recorded Since there was no demonstrated increase in blood flow and since oxygen delivery was decreased by hemodilution this is presumably another example of a paradoxical change in S T segment elevation Additional confusion has been generated by reports in which functional alterations in the myocardium have been shown to persist long after reversion of the epicardial electrocardiogram to normal[1] Holland and Brooks found that interpretation of the epicardial surface potential was complex and difficult and they suggested that conclusions based only upon epicardial S T segment mapping may not be accurate Muller and associates suggest that apparent paradoxical results obtained with the use of epicardial S T segment mapping can be ascribed to misinterpretation of changes in the overall QRS pattern They suggest that sites where severe ischemia results in QRS conduction delay cannot be interpreted in the same manner as ischemic sites without conduction delay In our experiments for example dog F exhibited a widened QRS at site I (S T = 13 mm) indicating severe ischemia but the ultrastructural morphology was not worse than that of site I_1 (S T = 4 mm.) Since regional myocardial blood flow is known to be quite variable in ischemic canine myocardium the finding that early ultrastructural changes do not correspond precisely to simultaneous epicardial maps should not be unexpected

Our study does not thus far address itself to the role of epicardial S T segment measurements in predicting the over all extent of myocardial injury for we have not examined the relationship between the sum of S T segment elevations and the over all ischemic changes in the myocardium The electrocardiogram recorded at a single point on the epicardium is likely to represent the influence of a much larger mass of muscle than that immediately underlying the mapping electrode If the entire ischemic zone were to be divided into columns of myocardium a three dimensional map of the ischemic portion of the ventricle could be constructed It is conceivable that such an anatomic map would then correlate closely with an over all epicardial S T segment map The preparation described in the present study of reversible ischemia should prove useful for further exploration of the relationships between the epicardial electrocardiogram and the underlying myocardium and for evaluating the effectiveness of interventions thought to be useful in the prevention and treatment of myocardial ischemic injury

Summary

A standardized preparation was developed to investigate the precise relationship between epicardial S T segment elevation and myocardial ultrastructure The distal left anterior descending coronary artery was occluded for 20 minutes and epicardial S T segments were recorded at five minute intervals Immediate perfusion-fixation with glutaraldehyde preserved premortem anatomic relationships and allowed precise sampling of the myocardium immediately underlying sites of S T segment recording Ischemic and non ischemic zones were defined both anatomically and by S-T segment mapping Transmural samples at 0.2 cm intervals were compared at sites in ischemic and non ischemic zones In non ischemic zones S T segment elevations ranged from 0 to 2 mm and myocardial ultrastructure was normal In ischemic zones S T segment elevations ranged from 0 to 14 mm and samples showed a gradient of ischemic injury with greatest change in subendocardial blocks The extent of ultrastructural change at any point was not consistently proportional to the height of S T segment elevation S T segment elevations greater than 2 mm were always associated with a marked transmural gradient of change but S T segment elevations less than 2 mm in ischemic zones could also be associated with severe subendocardial and mid myocardial change In a second group of dogs the coronary artery snare was released after 20 minutes of occlusion and recovery was allowed for 60 minutes before killing and subjecting to perfusion-fixation These

hearts exhibited no abnormality in myocardial ultrastructure when sampled in the same fashion as the first group

In this model a reproducible gradient of transmural myocardial ultrastructural change was demonstrated under conditions of reversible injury Prominent S T segment elevation in ischemic zones always indicated the presence of underlying ultrastructural change, but marked changes were also present when S T segment elevations were minimal, indicating that the S T segment maps tended to underestimate the extent of early ischemic change We were unable to establish a quantitative relationship between the extent of S T segment elevation and the extent of transmural ultrastructural change

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Dose independent pharmacokinetics of digoxin in humans

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The pharmacokinetics of digoxin in humans has been the subject of numerous investigations Most have focused on differences between individuals in digoxin disposition and on the effects of such factors as age weight sex renal function and disease states upon pharmacokinetics Few studies however have assessed the effect of digoxin dosage variations upon its pharmacokinetic properties within the same individual[1] The present study systematically investigated the pharmacokinetics of digoxin in healthy human subjects each of whom received the drug intravenously over a threefold range of doses

Methods

Subjects and procedure Nine healthy male volunteers participated in the study (Table I) All were free of identifiable medical disease were taking no medications on a chronic basis and had normal values of creatinine clearance

Each received three intravenous doses of digoxin (0 5 1 0 and 1 5 mg) in random sequence in a single dose three way crossover study with at least four weeks elapsing between drug exposures For each trial the appropriate dose was diluted to

Table I Subject characteristics

Subject number	*Age (years)*	*Weight (kg)*	*Creatinine clearance (ml/min/kg)*
1	33	69	1 81
2	33	90	1 4[illegible]
3	37	80	1 44
4	25	72	1 74
5	35	72	1 0[illegible]
6	3[illegible]	76	1 26
7	[illegible]0	8[illegible]	1.50
8	23	76	1 47
9	34	82	1 81
Mean (± SE)	31.3 (± 1.5)	77 (± 2.2)	1 50 (± 0 09)

30 ml with physiologic saline and infused intravenously into an antecubital vein over a period of one hour by a constant rate infusion pump Venous blood samples were drawn from the contralateral arm from an indwelling Butterfly cannula or by separate venipuncture prior to the infusion at the end of the infusion and the following times after the termination of the infusion 0 5 1 0 1 5 2 2 5 3 4 5 7 11 23 and 35 hours All urine was collected for a period of six days after the start of the infusion in 24 hour intervals Serum samples and aliquots of urine were frozen until the time of assay

Analysis of serum and urine Digoxin concentrations in all serum and urine samples were determined by radioimmunoassay

Analysis of data Post infusion serum digoxin concentration values were analyzed by weighted iterative nonlinear least squares regression tech

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Supported in part by Deutsche Forschungsgemeinschaft Bonn Bad Godesberg West Germany (Drs Ochs and Bodem) Grant MH [illegible] from the United States Public Health Service (Dr Greenblatt and Mr Harmatz) and by a grant from General Foods Corporation

Received for publication Jan 30 1978

Accepted for publication M[illegible] 16, 1978

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Lanoxin ampules, 0 25 mg ml, Boehringer Mannheim GmbH West Germany

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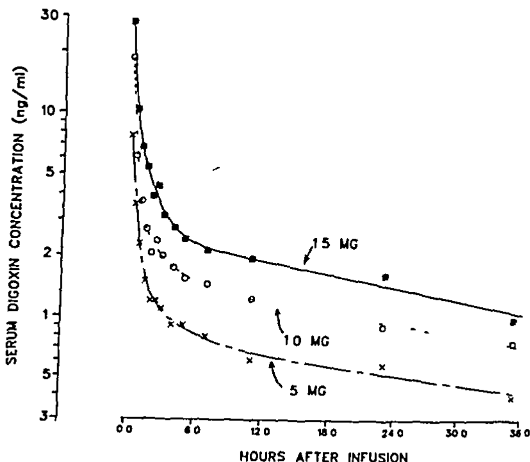


Fig 1 Serum digoxin concentrations following 0.5, 1.0 and 1.5 mg intravenous doses Each point is the mean for all subjects receiving the indicated dose at corresponding points in time Also shown are pharmacokinetic functions determined by nonlinear least squares regression analysis (Standard errors for individual data points were omitted for clarity and are available upon request from the authors)

niques[8, 9] Each set of data were fitted to the following two functions

$$C = Ae^{-\alpha t} + Be^{-\beta t} \quad (1)$$

$$C = Ae^{-\alpha t} + Pe^{-\pi t} + Be^{-\beta t} \quad (2)$$

where C is the serum concentration at time t after the end of the infusion The coefficients A, P, and B are hybrid intercept terms and were appropriately corrected for the infusion period[10], α, π and β are hybrid exponents For each set of data the choice between Equations 1 and 2 as functions of best fit was determined by comparison of the sum of squares of weighted residual errors for the two solutions and by assessment of the randomness of scatter of actual data points about the fitted function[11] The fitted functions were used to calculate the following pharmacokinetic variables[1, 11] distribution half life ($t_{1/2}\alpha$) elimination half life ($t_{1/2}\beta$) total apparent volume of distribution by the area method (V_d) and total clearance

The apparent urinary excretion half life of digoxin was calculated from logarithmic plots of average excretion rate versus midpoint of the collection interval Cumulative excretion projected to "infinite" time was determined using the apparent excretion half life and the excretion rate at the end of the 6 day collection period[13, 14] The renal clearance of digoxin was calculated as the product of total clearance and the fraction of the dose recovered in the urine projected to infinite time

The effect of dose upon pharmacokinetic variables was assessed by two way analysis of variance

Results

No subjective effects or untoward clinical experiences were reported by any of the volunteers during or after digoxin infusion

Disappearance of digoxin from serum was best described by Equation 1 in 20 of the 27 subject trials and by Equation 2 in the other seven Equation 2 best described disappearance of digoxin for the composite data points formed by across subject mean serum concentration values at corresponding points in time Fig 1 sh—

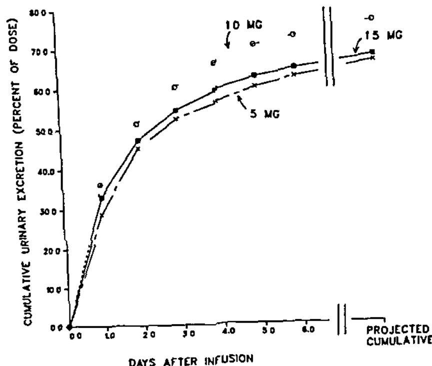


Fig 2 Urinary excretion of immunoassayable digoxin following 0.5 1.0 and 1.5 mg intravenous doses Each point is the mean for all subjects receiving the indicated dose at corresponding points in time (Standard errors for individual data points were omitted for clarity and are available upon request from the authors)

composite data points and functions of best fit Fig 2 shows mean values for urinary excretion of digoxin following the three doses

Table II shows pharmacokinetic variables at each of the three dose levels Two way analysis of variance indicated that dose had no significant effect upon any of these variables Mean renal clearance of digoxin did not differ significantly from creatinine clearance (paired t test = 0.98) and the two were not correlated (r = −0.06)

Discussion

Surveys of serum digoxin concentrations in patients receiving maintenance therapy generally suggest that steady state serum levels become higher with increasing doses [4,5] However the relation of digoxin dosage to digoxin clearance and/or steady state serum levels within the same individual has received relatively little attention and is not precisely established [5] The present study systematically assessed the disposition of intravenous digoxin in healthy subjects following 0.5 1.0 and 1.5 mg doses None of the identifiable pharmacokinetic variables changed significantly with dose suggesting that digoxin pharmacokinetics in healthy humans are dose independent over a relatively wide range of doses Further systematic studies of this type are needed in patients with cardiac disease

In the majority of our subjects disappearance of digoxin from serum was biexponential consistent with a two compartment open pharmacokinetic model In some cases the data were best described by a triexponential function consistent with a three compartment open pharmacokinetic model The triexponential pattern occurred randomly unassociated with a particular dose or a particular subject Both patterns are reported previously [2,21]

Kinetic variables for digoxin in our study are similar to those described previously [2,21,3] Digoxin distribution is extensive with apparent volumes of distribution averaging five to six times total body weight Our values of $t_{1/2}\beta$ at all three doses averaged 27 to 28 hours and thus are slightly shorter than the usually quoted value of 36 hours However the estimate of $t_{1/2}\beta$ can be influenced both by the duration of sampling

Table II Relation of digoxin pharmacokinetics to size of intravenous dose

Kinetic variable	Mean (±SE) values			Value of F (df = 2,16) from 2 way ANOVA*
	Dose			
	0.5 mg	1.0 mg	1.5 mg	
Distribution half life (hours)	0.45 (±0.08)	0.27 (±0.04)	0.32 (±0.09)	1.69
Elimination half life (hours)	28.0 (±5.2)	28.3 (±5.1)	27.4 (±3.7)	0.01
Volume of distribution (liters/Kg)	4.88 (±0.66)	5.98 (±0.96)	5.52 (±0.57)	0.50
Total clearance (ml/min/Kg)	2.38 (±0.48)	2.65 (±0.36)	2.50 (±0.21)	0.16
6 Day urinary excretion (per cent of dose)	61.4 (±6.7)	71.5 (±4.8)	63.5 (±4.2)	2.63
Urinary excretion half life (hours)	54.6 (±10.1)	37.9 (±5.1)	35.4 (±2.8)	2.67
Projected cumulative urinary excretion (per cent of dose)	67.7 (±6.8)	75.7 (±5.2)	66.8 (±4.4)	2.30
Renal clearance (ml/min/Kg)	1.50 (±0.24)	2.02 (±0.31)	1.62 (±0.12)	1.72

*For all values of F, p > 0.1

following a single dose,[4] as well as by the choice of pharmacokinetic model.[1] We measured serum digoxin concentrations for only 36 hours after a dose, which could have biased toward slightly shorter values of $t_{1/2}\beta$. This could also explain why urinary excretion half life values, based upon 6 days of sampling, were longer than serum elimination half lives.

Projected cumulative urinary excretion of digoxin by our subjects averaged no more than 76 per cent of the dose. Similar findings are reported by others.[1, 2] Thus, contrary to traditional teaching, a substantial fraction of a dose of digoxin is eliminated by extrarenal mechanisms. Renal clearance of digoxin in our study averaged 1.5 to 2.0 ml/min/Kg and did not differ significantly from creatinine clearance. The exact mechanism of renal excretion of digoxin is controversial,[5] but most studies indicate that values of renal clearance for digoxin and creatinine are similar or identical.[3-11]

Summary

Nine healthy male volunteers received single 0.5, 1.0, and 1.5 mg doses of intravenous digoxin in a randomized three way crossover study. Multiple venous blood samples were drawn during 35 hours after each dose and all urine was collected for 6 consecutive days. Concentrations of digoxin in serum and urine were determined by radioimmunoassay. Over all mean values for kinetic variables were: distribution half life 0.35 hours, elimination half life 27.9 hours, volume of distribution 5.46 liters/Kg, total clearance 2.51 ml/min/Kg. The mean projected cumulative urinary excretion of digoxin was 70.1 per cent of the dose; mean renal clearance of digoxin was 1.71 ml/min/Kg, not significantly different from creatinine clearance (1.50 ml/min/Kg). None of the identifiable pharmacokinetic variables was significantly influenced by dose, suggesting that digoxin disposition is dose independent in healthy individuals.

We are grateful for the assistance of Ann Werner and Dr. Dean S. MacLaughlin. Dr. MacLaughlin is supported in part by Grant GM 23430 from the United States Public Health Service to the Boston Collaborative Drug Surveillance Program.

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Origin of the basal systolic murmurs in mitral stenosis A study with intracardiac phonocardiography

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Intracardiac phonocardiography, introduced by Yamakawa and colleagues[1] in 1953, was a breakthrough in the realm of clinical phonocardiography Conventional external phonocardiography may not always reflect the acoustic events occurring in the cardiac chambers or great vessels In contrast intracardiac phonocardiography is able to obtain the vibratory events at the site of generation of murmurs

Functional or innocent murmurs are generally thought to originate in the pulmonary artery However, the earlier studies[2,3] were mostly confined to the right side of the heart A few intracardiac studies on the left side of the heart in normal subjects have demonstrated systolic murmurs within the aorta[4,5] Also, a specific type of innocent murmur has been thought to originate in the aorta near the aortic valve[6]

The basal systolic murmurs occasionally recorded in mitral stenosis have been so far regarded as occurring in the pulmonary artery just above the pulmonic valve[7] The purpose of the present study is to describe the origins of the basal systolic murmurs in mitral stenosis without other valvular diseases

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Accepted for publication Dec 1 1977
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Material and method

Left and right heart catheterization was carried out on 18 cases of mitral stenosis with basal systolic murmurs using a catheter tip micromanometer of Millar or a double lumen phonocatheter of American Electric Laboratory The age of subjects ranged from 20 to 48 years and the cardiac diagnosis, as shown in Table I was confirmed by heart catheterization and angiocardiography Both mitral and aortic regurgitations were excluded from the examined patients Of the 18 patients the diagnosis of 14 was eventually verified by surgical intervention

The hemodynamic data are shown in Table I in which there is no significant systolic pressure gradient across the aortic valve nor across the pulmonic valve

All procedures of heart catheterization were performed in the sedated and postabsorptive state after informed consent was obtained In the majority of cases a simultaneous recording of intracardiac and external phonocardiograms was made in conjunction with intracardiac pressure tracing with the aid of a Polygraph (Fukuda denshi MCM 8000) and a photographic recorder

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Table I Findings at catheterization

Case No	Name	Sex	Age	Diagnosis	PA cap press S/D (mean) mm Hg	Mean PA press S/D (mean) mm Hg	RV press S/D (mean) mm Hg	Aorta press S/D (mean) mm Hg	LV press S/D (mean) mm Hg
1	K.N	m	24	MS	12/2 (7)	24/8 (1?)	26/0 (8)	120/60 (80)	118/6 (44)
2	Y O	f	30	MS	3 /12 (??)	55/17 (30)	58 7 (18)	1?0/80 (95)	1?5/18 (60)
3	Y H	f	21	MS	28/16 (19)	34/18 (18)	4?/2 (20)	90/60 (70)	104/8 (42)
4	H.N	m	31	MS	?8/14 (19)	47/23 (22)	46/2 (15)	98/6? (82)	134/8 (38)
5	M.K.	m	42	MS	21/10 (15)	33/13 (?0)	41/4 (15)	1?9/ 0 (90)	100/6 (40)
6	Y.A	f	20	MS	27/?0 (24)	46/21 (33)	46/4 (??)	100/65 (77)	125/4 (45)
7	K T	m	32	MS	33/20 (?4)	44/20 (30)	?0/4 (?0)	118/?5 (90)	126/5 (40)
8	K.A.	m	?8	MS	30/20 (?6)	55/22 (?4)	56/6 (22)	125/60 (90)	118/11 (43)
9	H T	f	45	MS	30/1? (18)	54/?5 (33)	54/2 (20)	120/67 (82)	135/8 (40)
10	S I	f	38	MS	3?/17 (18)	60/35 (34)	60/5 (28)	135/78 (100)	110/4 (40)
11	M I	f	40	MS	20/10 (12)	30/13 (?0)	3?/2 (10)	110/60 (70)	118/6 (68)
12	S Y	f	39	MS	17/10 (13)	3?/10 (17)	38/? (19)	114/8? (90)	154/10 (65)
13	S K.	m	48	MS	30/16 (20)	42/20 (30)	40/2 (20)	151/102 (130)	110/4 (35)
14	Y.S	f	44	MS	18/14 (16)	40/15 (23)	40/3 (14)	110/?5 (65)	1?0/7 (40)
15	T O	f	44	MS	2?/10 (15)	33/15 (23)	3?/3 (1?)	12?/65 (90)	158/12 (75)
16	H I	f	34	MS	27/16 (20)	42/19 (26)	40/0 (16)	162/100 (120)	135/10 (62)
17	T.S	m	33	MS	14/9 (11)	30/13 (15)	32/4 (1?)	130/75 (100)	105/7 (44)
18	M.A	m	34	MS	26/13 (18)	29/10 (2?)	35/3 (13)	105/70 (82)	

Abbreviations MS = mitral stenosis m = male f = femal PA = pulmonary art ry CAP = capillary RV = right entricle LV = left entricl S = sy tou D = diastol

(Sanei sokki 100A) Paper speed was 100 mm /sec in the majority of cases

Intracardiac murmurs were explored in the pulmonary artery and the right ventricle and atrium on the right side of the heart and in the aorta just above the aortic valve and the left ventricle on the left side

Results

In this study we obtained ejection systolic murmurs in the aorta near the aortic valve the pulmonary artery and the outflow tract of the right ventricle using intracardiac phonocardiography of the left and right sides of the heart

I **Aortic origin** As shown in Table II an intra aortic systolic murmur was maximally *recorded* in 14 out of the 16 subjects having mitral stenosis with no clinical evidence of other valvular *diseases*. *In* these cases the ejection systolic murmur was definitely louder in the aorta than in the pulmonary artery On insertion of the phono catheter into the outflow tract of the left ventricle it disappeared or diminished in intensity The timing of this murmur ranged from early to mid systole and it was *crescendo–decrescendo* in configuration

Fig 1 shows intracardiac tracings obtained from a 44 year old patient with mitral stenosis (Y S) A loud ejection systolic murmur is recorded in the aorta *near the aortic valve* on the intracardiac phonocardiogram (I PCG) *in panel A* whereas there is no significant murmur in the main pulmonary artery *in panel B* Thus the basal systolic murmur in this case is thought to originate in the aorta near the aortic valve but not in the pulmonary artery

Fig 2 indicates another example of the ejection systolic murmur in the aorta in a 34 year old patient with mitral stenosis (H I) The intracardiac phonocardiogram shows an early systolic *murmur* in the aorta just above the valve However *there* was no loud systolic murmur in the main pulmonary artery Although the ascending branch of the aortic pressure tracing is slow *and* distorted there was no significant pressure gradient across the aortic valve in systole

II **Pulmonic origin** Two mitral stenosis patients showed the maximal *ejection* systolic murmur in the pulmonary artery whereas in the aorta only a slight systolic murmur was recorded

Fig 3 shows an ejection systolic *murmur* in the pulmonary artery in a 48 year old patient (S K) This case showed an ejection systolic murmur

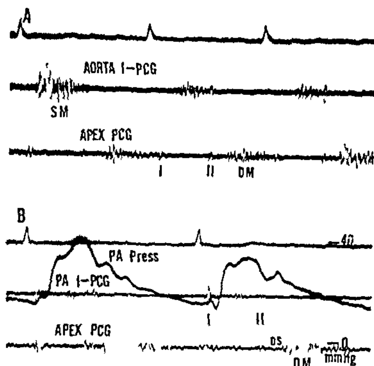


Fig 1 Intracardiac phonocardiograms obtained from a 44 year old patient with mitral stenosis (Y S) A loud ejection systolic murmur is noted in the aorta near the aortic valve (panel A) whereas there is no significant systolic murmur in the main pulmonary artery (panel B) Thus the basal systolic murmur probably originates in the aorta near the aortic valve I PCG = intracardiac phonocardiogram PCG = external phonocardiogram PA = pulmonary artery SM = systolic murmur DM = diastolic murmur I = first heart sound II = second heart sound OS = mitral opening snap Press = pressure

(Grade 2/6) at the second left intercostal space on the chest wall In the intracardiac phonocardiogram, an ejection systolic murmur is shown in the pulmonary artery, accompanied by a small, early diastolic murmur However the systolic murmur was less loud in the aorta Thus the main pulmonary artery is thought to be the origin of this murmur

III Right ventricular origin In two cases a late systolic murmur was obtained from the outflow tract of the right ventricle and it diminished in the pulmonary artery and the aorta As a result, we postulate here that the outflow tract of the right ventricle is another origin of the basal systolic murmur in mitral stenosis although it was not so loud on the chest wall Fig 4 shows a loud systolic murmur in the outflow tract of the right ventricle in a 45 year old female with mitral stenosis (H T) A late systolic murmur is noted on the intracardiac phonocardiogram of the right ventricular outflow tract

Table II Intracardiac location of the basal systolic murmurs in mitral stenosis

Case No	Name	Sex	Age	Diagnosis	Location of systolic murmur		
					Aorta	PA	RV outflow
1	KN	m	24	MS†	++	–	–
2	YO	f	30	MS	++	–	–
3	YH	f	21	MS	++	+	–
4	HN	m	31	MS	++	+	–
5	MK	m	42	MS	+	–	–
6	YA	f	20	MS	+	+	++
7	KT	m	32	MS	+	–	–
8	KA	m	28	MS	+	–	–
9	HT	f	45	MS	+	+	++
10	SI	f	38	MS	–	++	–
11	MI	f	40	MS	++	–	–
12	SY	f	39	MS	++	–	–
13	SK	m	48	MS	+	++	–
14	YS	f	44	MS	++	+	–
15	TO	f	44	MS	++	+	–
16	HI	f	34	MS	++	+	–
17	TS	m	33	MS	+	–	–
18	MA	m	34	MS	+	–	–

Of the 18 patients with mitral stenosis, 14 showed the maximum systolic murmur in the aorta near the aortic valve whereas in two cases the loud ejection systolic murmur was recorded in the main pulmonary artery In the other two cases a late systolic murmur was maximally recorded in the outflow tract of the right ventricle

†Abbreviations and symbols MS = mitral stenosis PA = pulmonary artery RV = right ventricle ++ = loud systolic murmur + = slight systolic murmur m = male f = female

Discussion

Our observations showed that the basal systolic murmur in mitral stenosis without associated valvular diseases originated mostly in the aorta and in a few cases in the pulmonary artery and the outflow tract of the right ventricle

According to the study by Kunos and associates[7] the basal systolic murmur in mitral stenosis was derived from the acoustic events in the pulmonary artery, and was elucidated by relative pulmonic stenosis On the other hand, Stuckey[8] has reported that the majority of the innocent murmurs may have an aortic origin The etiology of this systolic murmur is suggested by its timing which corresponds to that of the maximum ejection of blood from the ventricles This was not proved however, by the intracardiac sound analysis

In earlier studies[2, 3] with intracardiac phonocardiography, the ejection systolic murmur in

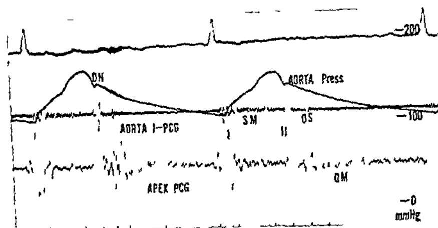


Fig 2 Intra arterial sound and pressure tracing simultaneously recorded with external phonocardiogram in a 34 year old subject with mitral stenosis (H I) An early systolic murmur is recognized in the aorta just above the aortic valve However no loud systolic murmur was noted in the main pulmonary artery The ascending branch of the aortic pressure tracing is slow and distorted although there was no significant pressure gradient across the aortic valve in systole It may be due to a technical artifact *I PCG* = intracardiac phonocardiogram *PCG* = external phonocardiogram *SM* = *systolic murmur* *DM* = *diastolic murmur* *I* = first heart sound *II* = second heart sound *DN* = dicrotic notch *OS* = mitral opening snap *Press* = pressure

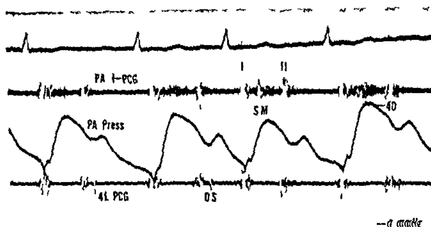


Fig 3 An ejection systolic murmur in the pulmonary artery This tracing was obtained from a 48 year old patient with mitral stenosis (S K) The loudest ejection systolic murmur is recorded on the phonocardiogram of the main pulmonary artery accompanied by a small early diastolic murmur The systolic murmur is thought to originate in the pulmonary artery since it was less loud in the aorta *I PCG* = intracardiac phonocardiogram *PCC* = external phonocardiogram *PA* = pulmonary artery *SM* = systolic murmur *DM* = diastolic murmur *I* = first heart sound *II* = second heart sound *OS* = opening snap *4L* = the fourth left intercostal space *Press.* = pressure

normal subjects was regarded to occur in the pulmonary artery However these studies were mainly confined to the intracardiac events of the right side of the heart In contrast a few intracardiac studies, in the left side of the heart in normal subjects have demonstrated systolic murmurs within the aorta and the innocent vibratory murmur has been thought to originate near the aortic valve

Recently Stein and Sabbah showed that disturbed blood flow with a turbulent energy density about one third of that of patients with aortic insufficiency is found in the ascending aorta of patients with a normal aortic valve Subsequently studies of turbulent blood flow and ejection systolic murmurs have shown a linear relation between the intensity of the intraarterially recorded murmurs and turbulent power

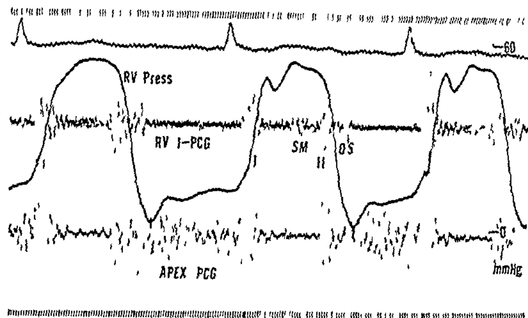


Fig 4 A late systolic murmur in the outflow tract of the right ventricle The intracardiac sound was obtained from a 45 year old patient with mitral stenosis (H T) A late systolic murmur is clearly noted in the outflow tract of the right ventricle whereas there was no loud murmur in the pulmonary artery and the aorta A functional infundibular stenosis may be closely related to the turbulence of blood flow in the right ventricular outflow tract which is responsible for the genesis of the late systolic murmur RV = right ventricle Other abbreviations are the same as in Fig 1

production, thus demonstrating a clear association between the magnitude of turbulent flow and ejection systolic murmurs Moreover, their preliminary studies[10] have shown that turbulence in patients without valve disease occurs with greater intensity in the aorta than in the pulmonary artery The reason that turbulence is greater within the aorta may be related to the more compliant walls of the pulmonary artery which may have a damping effect upon turbulence

More recently, Stein and Sabbah[11] reported that the intensity of the intraarterial sound was greater above the aortic than above the pulmonary valve These findings suggest that innocent murmurs may be of aortic origin, which led us to undertake this study on the origin of the basal systolic murmurs in mitral stenosis

The majority of our patients showed systolic murmurs in the aorta rather than in the pulmonary artery, in spite of no significant systolic pressure gradients across the aortic valve Similar to the mechanism of production of innocent murmur the turbulence in the aorta is probably greater than in the pulmonary artery These systolic murmurs are thought to occur due to the turbulence within the aorta and may be functional or organo functional since the aortic valve in mitral stenosis occasionally shows a rheumatic change which may not produce pressure gradients

With regard to the second origin of the basal systolic murmur, we noted a loud ejection systolic murmur in the main pulmonary artery of two mitral stenosis patients, whereas there was less loud bruit in the aorta near the aortic valve No significant pressure gradients across the pulmonic valve were noted in systole The ejection systolic murmur is thought to occur due to the turbulence of blood flow produced by the dilated pulmonary artery

Next the outflow tract of the right ventricle is also regarded as another origin of the basal systolic murmur We encountered a late systolic murmur during exploration of the right ventricle with phonocatheter Till now a study using intracardiac phonocardiography in which the late systolic murmur emanates from the right ventricular outflow tract in mitral stenosis has never been reported

Auinger and associates[12] reported that the expiratory compression of the right ventricular outflow tract by the thoracic wall was responsible for the production of the basal systolic murmur in mitral stenosis Moreover Leatham[13] mentioned that the physiological ejection systolic murmur found in normal children probably originates

from the right ventricular outflow tract because of its adjacency to the stethoscope though vibrations can be recorded in both right and left outflow tracts by intracardiac phonocardiography In moderate to severe valvular pulmonic stenosis Kambe and associates[14] pointed out that a late systolic murmur occurred in the right ventricular outflow tract due to functional infundibular stenosis

It is our opinion that the late systolic murmur in mitral stenosis is most likely to occur due to functional or relative stenosis of the right ventricular outflow tract The term functional murmur[15] may be applied to those basal systolic murmurs originating from the cardiovascular system mentioned above

In general intracardiac phonocardiography is most useful to localize cardiac murmurs and sounds. A major advantage of this method is that it may detect even a small eddy not audible as a murmur on the chest wall However it may produce an artificial turbulence in the heart in addition to already existing murmurs Moreover a positional gap may occur between the turbulence of blood flow and the axis of the sensitive element However intracardiac phonocardiography though invasive is thought to be most useful to localize the basal systolic murmurs in mitral stenosis

Summary

In order to study the origin of the basal systolic murmurs in mitral stenosis left and right heart catheterization was performed in 18 patients with mitral stenosis using intracardiac phonocardiography Our data revealed that the basal systolic murmurs originated in the aorta the pulmonary artery and the outflow tract of the right ventricle

In 14 cases we noted the maximal ejection systolic murmur in the aorta near the aortic valve However in two cases there was a loud systolic murmur in the pulmonary artery These murmurs occurred in early to mid systole and were crescendo-decrescendo in configuration The pitch of the murmur ranged from low to medium frequency in the majority of cases They are produced by the turbulence of blood flow in the aorta and the pulmonary artery

A late systolic murmur was also recorded in the outflow tract of the right ventricle in two patients This is thought to occur due to functional or relative infundibular stenosis of the right ventricle It differs in location and timing from those in the aorta and the pulmonary artery The outflow tract of the right ventricle is regarded as the third origin of the basal systolic murmur in mitral stenosis

We thank Mr Yoshihisa Kitamura for his technical assistance

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The nonınterference of aluminum hydroxıde gel wıth quınıdıne sulfate absorptıon An approach to control quınıdıne-ınduced dıarrhea

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Quınıdıne has been used ın the successful treatment of cardıac arrhythmıas for over two decades However ıts toxıcıty, ıncludıng nausea vomıtıng dıarrhea and more serıous problems of arrhythmıas and sudden death has lımıted ıts usefulness ın certaın sıtuatıons Of partıcular note ıs the gastroıntestınal ıntolerance that many patıents experıence It ıs estımated that nausea vomıtıng, and dıarrhea occur ın 30 per cent of patıents ıngestıng quınıdıne requırıng dıscontınuatıon of therapy ın as many as 10 per cent[1-3] These sıde effects are not related to dose or to blood levels They are belıeved to be due to a dırect stımulant actıon on the smooth muscle of the small ıntestıne[4]

We have encountered patıents who have requıred quınıdıne for the successful control of theır arrhythmıas but who could not tolerate the resultıng gastroıntestınal symptoms partıcularly dıarrhea Concomıtant admınıstratıon of alumınum hydroxıde gel wıth theır quınıdıne dose resulted ın reductıon of dıarrhea wıth apparently contınued control of theır arrhythmıas

Prevıous reports of ınterference wıth drug absorptıon by antacıds prompted a study to determıne the effects of alumınum hydroxıde gel on quınıdıne absorptıon

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Receıved for publıcatıon Oct 13 1977

Accepted for publıcatıon Nov 21 1977

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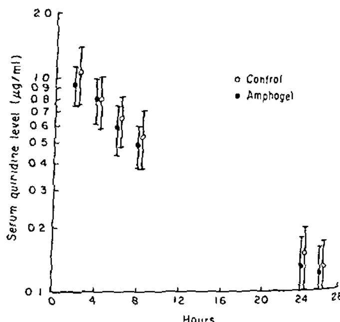


Fıg 1 Comparıson of concentratıon verses tıme curves of quınıdıne sulfate admınıstered wıth alumınum hydroxıde gel or water ın four normal volunteers Brackets ındıcate ±1 SEM

Methodology

Four healthy volunteers rangıng ın age from 28 to 42 years ıngested 200 mg of quınıdıne sulfate and 30 mıllılıters of alumınum hydroxıde gel (Amphogel antacıd trıal) or water (placebo trıal) after an overnıght fast The alumınum hydroxıde gel was ıngested concomıtantly wıth and a second 30 ml dose one hour after quınıdıne sulfate Blood samplıng for quınıdıne was obtaıned at 2 4 6 8, 24 and 26 hours after drug ıngestıon Twenty four hour urıne collectıons for quınıdıne and pH determınatıons were obtaıned

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After a two week washout period the experiment was repeated. Volunteers receiving antacid were given placebo and those receiving placebo were given antacid, using a randomized cross over design.

Assay

Quinidine was quantitated by the Kessler and associates modification of the method of Cramer and Isaksson. Briefly, to a 12 ml centrifuge tube 0.5 ml serum, 0.5 ml 0.1N NaOH, and 5 ml benzene are added. The contents of the tube are mixed with a vortex type mixer and centrifuged. The organic phase is transferred after the addition of 0.2 ml isoamyl alcohol to a new centrifuge tube containing 3 ml of 0.1 N H_2SO_4. After mixing and subsequent centrifugation the fluorescence of the acid phase is read in an Aminco Bowman spectrophotofluorometer at an excitation wavelength of 340 nm and an emission wavelength of 450 nm.

Results

The results of this study are presented in Fig. 1 and Table I. No significant differences in quinidine levels were seen in the concentration verses time plots, the two curves appearing almost superimposable. This is confirmed by the lack of significant difference in the area under curve determinations (Table I). This indicates no impairment of absorption of quinidine by aluminum hydroxide gel. The urine pH during the antacid trial ranged from 5.0 to 6.2 with a mean of 5.7. During the placebo trial the urine pH ranged from 5.0 to 6.0 with a mean of 5.5. The average cumulative excretion of quinidine over 24 hours after the antacid trial was 19 per cent of the dose and after the placebo trial was 18 per cent.

Discussion

The effects of antacids on the absorption of drugs has been studied to a limited extent.[5, 6] Antacids may alter the absorption of medications administered concomitantly. Our study shows that aluminum hydroxide gel does not interfere with the absorption of quinidine sulfate.

Aluminum hydroxide gel has been given to treat the diarrhea associated with quinidine administration. We have thus far encountered four patients whose arrhythmias were controlled by quinidine but who developed diarrhea secondary to quinidine ingestion. In three, aluminum hydroxide gel was successful in controlling this effect; in the fourth a reduction in stool frequency to tolerable levels was achieved. In all cases control of the arrhythmia was maintained without altering the dose of quinidine.

The mechanism for diarrhea induced by quinidine is unknown at present but may be due to local stimulant effect on intestinal motility. Studies in canines have demonstrated that quinidine increases the frequency of fast or spike potentials in the small intestine and colon.[4] These potentials correlate with increases in intestinal contraction. Thus quinidine may exert its diarrhogenic effect by increasing intestinal tone and motility.

Aluminum hydroxide is known to delay gastric emptying time both in animals and man.[8] This action is mediated by the action of aluminum ion. It has been demonstrated that intraluminally applied aluminum solution inhibits contractions elicited by serosally administered acetylcholine both in rat and human gastric smooth muscle.[9] It is therefore possible that the effect of quinidine on increasing intestinal motility is blocked by the smooth muscle relaxing effect of the aluminum ion, resulting in control of diarrhea.

Table I. Areas under curve expressed as mcg./ml./hr. calculated by the trapezoidal rule

Subject	*Placebo*	*Amphogel*
1	308	326
2	266	236
3	429	472
4	497	395
Mean	375	357
SD	107	100

Not significantly different (P > 01).

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Noninvasive diagnosis of ischemic cardiomyopathy by fluoroscopic detection of coronary artery calcification

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Severe coronary artery disease may give rise to progressive cardiomegaly and congestive heart failure[1] In the absence of a clear history of myocardial infarction the resulting ischemic cardiomyopathy may be difficult to distinguish from nonischemic cardiomyopathy Since the clinical course and management of ischemic and nonischemic cardiomyopathy may differ it is important to identify accurately these two clinical entities While coronary arteriography has been used to make this differential diagnosis it would be desirable to have a reliable noninvasive method Both echocardiography[2-4] and thallium 201 perfusion imaging recently have been employed to separate patients with severe left ventricular dysfunction and a history of myocardial infarction from those with nonischemic cardiomyopathy However this distinction can be made readily from the clinical history and it remains to be seen whether either technique can ascertain the diagnosis in the patient with cardiomyopathy in whom the presence or absence of significant coronary artery disease cannot be determined by routine clinical evaluation In this report the clinical hemodynamic and angiographic data in 24 patients presenting with severe congestive heart failure and cardiomegaly of unknown etiology are reviewed and it is shown that identification of coronary arterial calcification by fluoroscopy provides a reliable means of distinguishing those with ischemic from those with nonischemic cardiomyopathy

Methods

The study group was derived from those patients presenting to the San Diego Veterans Administration Hospital with severe congestive heart failure and cardiomegaly who underwent diagnostic cardiac catheterization and coronary arteriography between July 1974 and July 1977 Patients with a history of myocardial infarction were excluded prior to catheterization and patients found to have significant valvular lesions were excluded following catheterization The 24 remaining patients none of whom had a history of excessive alcohol intake constituted the study group Prior to left ventriculography and coronary arteriography all patients underwent cardiac fluoroscopy with cesium iodide image intensification in the anteroposterior left anterior oblique and right anterior oblique projections All studies were performed by one fluoroscopist (A D J) with observation and verification by a second physician who was in attendance The findings on fluoroscopy were then compared with the results of coronary arteriography performed by either the Sones or Judkins techniques A 75 per cent or greater reduction in cross-sectional area of at least one major coronary vessel was required for a diagnosis of significant coronary disease

Biplane left ventriculograms were obtained

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Received for publication Oct 24 1977

Accepted for publication Dec 1 1977

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Table I Clinical, hemodynamic angiographic and fluoroscopic data from 24 patients

Patient*		Age	Risk factors	Chest pain		Electrocardiogram				LV function		Coronary arteriography			Coronary calcification		
				Typ†	Atyp	Q	LBBB	RBBB	LVH	LVEDI	EF	RT	LAD	CIRC	RT	LAD	CIRC
Ischemic Cardiomyopathy																	
1	GC	63	+						+	198	29	+	+		+	+	
2	HR	42	+	+		+				102	21		+	+	+	+	+
3	AC	46	+		+					117	22	+	+	+	+	+	+
4	MW	54	+	+		+				110	18		+			+	+
5	CF	50					+			122	28	+	+		+	+	
6	GB	39	+		+	+				125	25	+	+		+	+	
7	AC	53	+		+					177	13	+	+		+	+	+
8	HM	51								136	35	+	+	+	+	+	+
9	RW	68	+							147	25	+	+		+	+	+
10	RC	58	+							100	32	+	+	+	+	+	+
Non ischemic Cardiomyopathy																	
11	KK	26	+		+	+				150	16		Normal			Absent	
12	DA	42	+	+		+				124	19		Normal			Absent	
13	HS	57			+	+				160	22		Normal			Absent	
14	DP	34	+							101	32		Normal			Absent	
15	SN	54	+			+				158	29		Normal			Absent	
16	WK	46						+		156	20		Normal			Absent	
17	BB	27				+				166	10		Normal			Absent	
18	DT	31							+	150	15		Normal			Absent	
19	PO	42								122	19		Normal			Absent	
20	RD	26	+							150	15		Normal			Absent	
21	EW	50	+				+			171	26		Normal			Absent	
22	CL	60					+			189	24		Normal			Absent	
23	WR	56	+					+		116	32		Normal			Absent	
24	MC	62	+			+				251	34		Normal			Absent	

Patients 1 10 abnormal coronary arteriograms patients 11 24 normal coronary arteriograms
†Abbreviations Typ = typical ischemic chest pain Atyp = atypical ischemic chest pain LVEDI = end-diastolic volume index EF = ejection fraction

using standard techniques Ejection fraction and left ventricular end diastolic volume index (LVEDI) were calculated using volumes deter mined by the area-length method [8]

All patients were then characterized with respect to their clinical electrocardiographic and hemodynamic findings as summarized in Table I Those patients with abnormal coronary arterio grams were considered to have ischemic cardio myopathy, while those with normal coronary arteriograms were considered to have a form of nonischemic cardiomyopathy

Student s t test was used for comparison of clinical hemodynamic and angiographic data between the two groups of patients

Results

Coronary arteriography Ten patients were found to have abnormal coronary arteriograms Six had triple vessel disease three had double vessel disease and all had significant lesions of the left anterior descending coronary artery These ten patients were considered to have ischemic myocardial disease The remaining 14 patients had unequivocally normal coronary arteriograms and were given the diagnosis of nonischemic cardiomyopathy

Hemodynamic findings All 24 patients showed evidence of significant hemodynamic compromise No patient had a left ventricular end diastolic volume index less than 100 c c /M , and no patient had an ejection fraction greater than 35 As shown in Table II the mean left ventricular end diastolic volume index was somewhat greater in the nonischemic group and the mean ejection fraction somewhat lower However, the differ ences between the two groups were not statisti cally significant The left ventriculograms of all

Table II Comparison of clinical and hemodynamic characteristics

	No	Mean age (yrs)	Mean LVEDI (ml/M)	Mean EF	Risk Factors	Chest pain	ECG Q waves
Ischemic cardiomyopathy	10	52	133	25	80%	50%	30%
Nonischemic cardiomyopathy	14	44	154	20	57%	30%	43%

A given patient was included in this category if the clinical history revealed smoking hypertension diabetes or posit family history for myocardial infarction No patient in either group was diabetic

24 patients showed diffuse hypokinesis with no evidence of a discrete left ventricular aneurysm

Clinical history The mean ages of the patients in the two groups did not differ significantly although no patient with ischemic cardiomyopathy was less than 39 years of age Chest pain typical or atypical for angina pectoris and the presence of at least one coronary risk factor (see Table II) were more common in those patients with ischemic cardiomyopathy However these features were not unique to the patients with ischemic cardiomyopathy as they were present in a significant fraction of the patients with normal coronary arteriograms

Electrocardiogram The presence of significant Q waves (≥ 04 seconds duration) on the ECG was not a distinguishing characteristic of the patients with ischemic cardiomyopathy Indeed they were more common in the group with nonischemic cardiomyopathy

Fluoroscopy All ten patients with significant coronary disease had coronary artery calcification identified on fluoroscopy Each had calcification in the region of the left anterior descending coronary artery three had calcium present in the region of two major coronary arteries and six patients had calcification in each of the three major coronary vessels None of the 14 patients with normal coronary angiograms (nonischemic cardiomyopathy) had coronary calcification identified by fluoroscopy

Discussion

Burch and co workers have used the term "ischemic cardiomyopathy to describe a class of patients with severe myocardial dysfunction and coronary artery disease With a carefully obtained clinical history many patients with ischemic cardiomyopathy may be distinguished by the occurrence of a previous myocardial infarction or angina pectoris Nevertheless there remains a group of patients with ischemic heart disease such as the one presented in this study which cannot be clearly distinguished from patients with idiopathic cardiomyopathy on the basis of the clinical history or electrocardiogram No patient gave a history of myocardial infarction While coronary risk factors and chest pain were more frequent in the ten patients with ischemic cardiomyopathy they were also found in the patients with nonischemic cardiomyopathy The presence of Q waves on the electrocardiogram was neither a sensitive nor a specific indicator of ischemic disease Other studies have shown that patients with nonischemic cardiomyopathy commonly demonstrate Q waves[9] Furthermore the frequent occurrence of left bundle branch block or left ventricular hypertrophy can obscure the electrocardiographic diagnosis of prior myocardial infarction in this setting

Fluoroscopic examination of the coronary arteries for calcification offers an appealing method for differentiating ischemic from nonischemic cardiomyopathy without coronary arteriography The work of Bartel and associates[1] has demonstrated that this technique when carefully performed can detect coronary artery calcification in the majority of patients with two or three vessel coronary disease giving few false positives All of the patients with ischemic cardiomyopathy in our study had coronary artery calcification easily detected by fluoroscopy The remarkable sensitivity of cardiac fluoroscopy in these hemodynamically compromised patients may be related to the severity of their underlying coronary disease None of our patients with cardiomyopathy and normal coronary arteriograms had coronary artery calcification which indicates that fluoroscopic detection of coronary calcification was a highly specific marker for ischemic cardiomyopathy in the population of patients studied

In conclusion we recommend that cardiac

Table I Clinical, hemodynamic, angiographic, and fluoroscopic data from 24 patients

Patient		Age	Risk factors	Chest pain		Electrocardiogram				LV function		Coronary arteriography			Coronary calcification		
				Typ†	Atyp	Q	LBBB	RBBB	LVH	LVEDI	EF	RT	LAD	CIRC	RT	LAD	CIRC
Ischemic Cardiomyopathy																	
1	GC	63	+						+	198	29	+	+		+	+	
2	HR	42	+	+		+				102	21		+	+	+	+	+
3	AC	46	+		+					117	22	+	+	+	+	+	+
4	MW	54	+	+		+				110	18		+			+	+
5	CF	50					+			122	28	+	+		+	+	
6	GB	39	+		+	+				125	25	+	+		+	+	
7	AC	53	+		+					177	13	+	+		+	+	+
8	HM	51								136	35	+	+	+	+	+	+
9	RW	68	+							147	25	+	+		+	+	+
10	RC	58	+							100	32	+	+	+	+	+	+
Non ischemic Cardiomyopathy																	
11	KK	26	+		+	+				150	16		Normal			Absent	
12	DA	42	+	+		+				124	19		Normal			Absent	
13	HS	57			+	+				160	22		Normal			Absent	
14	DP	34	+							101	32		Normal			Absent	
15	SN	54	+			+				158	29		Normal			Absent	
16	WK	46						+		156	20		Normal			Absent	
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Echocardiographic detection of a subannular aortic aneurysm*

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Subannular aortic aneurysms have been reported in a number of clinical and autopsy studies[1,2] In most cases the diagnosis was made incidentally either at surgery or at postmortem examination[3] On occasion the diagnosis has been made by angiography Echocardiograms on a patient with aortic and mitral insufficiency suggested the possibility of such an aneurysm The aneurysm was subsequently demonstrated by angiography and confirmed at surgery

Case report

A 24 year-old white female was admitted to the hospital with *complaints of* nonspecific precordial chest discomfort low grade fever nonproductive cough and malaise There was no history of rheumatic fever or intravenous drug use Evaluation including multiple blood cultures yielded no specific diagnosis. The patient s symptoms improved without therapy However during follow up examination four weeks later previously undetected murmurs of aortic and mitral insufficiency were heard and signs of mild congestive heart failure were noted Multiple blood cultures serological tests and skin tests were negative A presumptive diagnosis of bacterial endocarditis was made and a four week course of penicillin and streptomycin was administered Nonetheless the patient developed worsening congestive heart failure associated with clinically severe aortic and mitral regurgitation and was scheduled for cardiac catheterization An echocardiogram was performed from the standard fourth left intercostal space using a 2.25 mHz transducer a Smith Kline Industries Ekoline 20A scanner and a Honeywell 1858 fiberoptic strip chart recorder Abnormal dense echoes were recorded behind the posterior aortic wall. The line of echoes moved abruptly posterior at th onset of systole and then moved anteriorly parallel to the posterior aortic wall (Fig 1) The motion of the echoes suggested a chamber posterior to the aorta expanding in systole and emptying in diastole Transesophageal echocardiography was performed with an Aerotech 3 5 mHz transesophageal transducer using the same scanner and strip chart recorder The transesophageal echocardiogram revealed identical abnormal echoes behind the posterior aortic wall (Fig 2)

Angiography performed at cardiac catheterization revealed an enlarged left ventricle and severe mitral and aortic insufficiency There was a large aneurysm posterior to the aorta with its orifice beneath the left aortic cu p The aneurysm filled during ventricular systole and emptied during diastole The motion of the posterior wall of the aneurysm was consistent with the motion of the abnormal echoes noted on the echocardiograms. In addition to the large posterior aneurysm there were two smaller aneurysms one in the left sinus of Valsalva below th origin of the left coronary artery and a second adjacent to the mitral annulus (Fig 3)

At operation, the mitral valve was exposed through the left atrium and the aortic valve through the aorta The anterior leaflet of the mitral valve was completely flail secondary to extensive chordal rupture The mitral valve was replaced with a Bjork Shiley prosthesis The aortic valve leaflets were normal. A 3 mm opening was found in the left coronary sinus of Valsalva which led to an aneurysmal pocket posteriorly A similar but larger orifice (6 mm) was identified under the aortic annulus just below the commissure between the noncoronary and left coronary leaflets This orifice communicated with a second aneurysm which was larger and inseparable from the left atrium (Fig 4) Repair of these lesions was impossible without significant distortion of the aortic valve Therefore the aortic valve was excised and the orifices were

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Received for public tion Sept 7 1977

Accepted f r public ti n Oct. 31 1977

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*The opinions or assertions contained herein are the private views of the a thors and are not to be construed as reflecting the views of the Department f the Army or th Departm nt of Def nse

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fluoroscopy, with image intensification to detect the presence or absence of coronary calcification be performed in all patients presenting with congestive heart failure of unknown etiology This technique provides a simple, noninvasive, reliable, and economical means of differentiating patients with ischemic cardiomyopathy from those with idiopathic myocardial disease

Summary

Twenty four patients with severe congestive heart failure and cardiomegaly in whom the presence or absence of significant coronary disease could not be ascertained clinically under went fluoroscopy for coronary artery calcification prior to cardiac catheterization Ten of the patients were found to have significant coronary artery disease, and 14 had normal coronary arteriograms Coronary artery calcification was found in all ten patients with significant coronary disease and was absent in all of those patients *with normal coronary arteriograms We conclude* that fluoroscopy for coronary artery calcification provides a reliable noninvasive method for differ entiating ischemic from nonischemic cardiomyop athy

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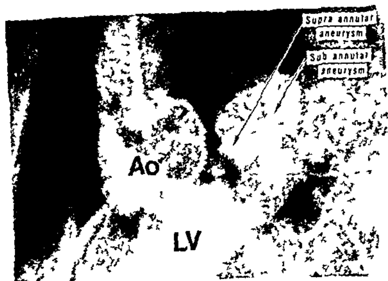


Fig 3 Aortic root angiogram lateral projection A large aneurysm with a subannular origin is noted A small supra-annular aneurysm can also be seen The small aneurysm adjacent to the mitral valve is not seen in this view *Ao* = aorta *LV* = left ventricle

of the aneurysm was noted to be subvalvular In the current case both the transthoracic and transesophageal echocardiograms clearly demonstrated a posterior chamber between the aorta and left atrium which increased in size in early systole and decreased in diastole strongly suggesting the presence of an aneurysm The angiogram confirmed its presence and delineated its subannular origin

This case confirms the usefulness of echocardiography in detection of subannular aortic aneurysms and its indication for evaluating the aortic outflow area in patients with aortic valve disease especially when endocarditis is either proved or suspected In addition transesophageal echocardiography was demonstrated to be useful in evaluating the aortic outflow tract for this particular abnormality and may be indicated in the assessment of patients in whom external echocardiography is technically suboptimal Angiography remains the ultimate technique for confirming the presence and exact location of such aneurysm

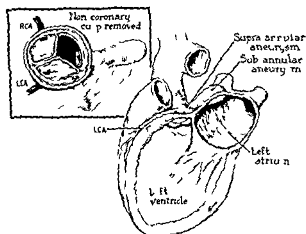


Fig 4 Illustration of the two aneurysms as seen at surgery The orifice of the large subannular aneurysm is below the valve at the junction of the noncoronary and left coronary cusps The origin of the supra annular aneurysm is in the left coronary cusp *LCA* = left coronary artery *RCA* = right coronary artery

Summary

A subannular aortic aneurysm was detected on standard and transesophageal echocardiograms obtained from a patient with severe aortic and mitral regurgitation The presumed etiology was bacterial endocarditis A brief discussion of subannular aneurysms is presented along with pertinent material from this case

The authors wish to thank Gregory Snyder for his technical expertise George Thomas for his illustration and Bettye Jo Hairston for her editorial assistance

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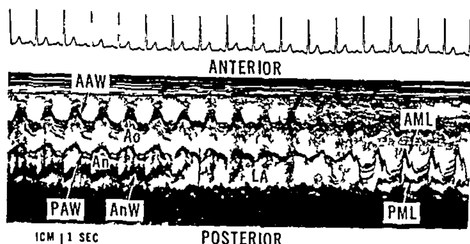


Fig 1 Standard echocardiogram demonstrating a sweep from mitral valve to aorta A dense line of echoes representing the aneurysm wall *(AnW)* is noted posterior to the aorta *(Ao)* *AAW* = anterior aortic wall *AML* = anterior mitral leaflet *An* = aneurysm *LA* = left atrium *PAW* = posterior aortic wall *PML* = posterior mitral leaflet

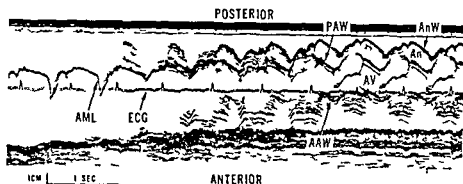


Fig 2 Transesophageal echocardiogram demonstrating a sweep from anterior mitral leaflet *(AML)* to aorta The top of the figure is posterior The aneurysm *(An)* is clearly defined posterior to the aorta *AAW* = anterior aortic wall *AnW* = aneurysm wall *AV* = aortic valve *ECG* = electrocardiogram *PAW* = posterior aortic wall

closed with buttressed sutures which were incorporated into the sewing ring of a Bjork Shiley aortic valve The aneurysm adjacent to the mitral annulus visualized on angiography was not found The patient was removed from cardiopulmonary bypass without difficulty and her postoperative course was uncomplicated

Discussion

Subannular aortic aneurysms arise in the fibrous connective tissue supporting the aortic and mitral valves The exact etiology of these aneurysms is unknown There is strong support for the concept of congenital weakness of the fibrous skeleton of the valve rings with subsequent aneurysm formation [1 9 12] In addition, cases of aneurysms have been reported following episodes of bacterial and fungal endocarditis [3 5] and following trauma [6] Endocarditis may or may not play a primary role in the formation of these aneurysms In the case presented, there was no histological evidence of endocarditis on either the aortic or mitral valve leaflets Aortic insufficiency was secondary to distortion of the valve created by the aneurysms, and the mitral insufficiency was secondary to rupture of the chordae tendineae Endocarditis is the presumed etiology in this case but it is by no means certain

Abnormalities of the aortic outflow tract and valve, including hypertrophic cardiomyopathy valvular subvalvular and supravalvular aortic stenosis sinus of Valsalva aneurysms, and aortic valve vegetations have well defined echocardiographic patterns A recent paper described dense interrupted echoes adjacent to the posterior wall of the aorta in a patient with endocarditis and aortic insufficiency An aneurysm was noted on angiography [11] Preoperatively, this was thought to represent an aneurysm of the noncoronary sinus of Valsalva however, at surgery the ostium

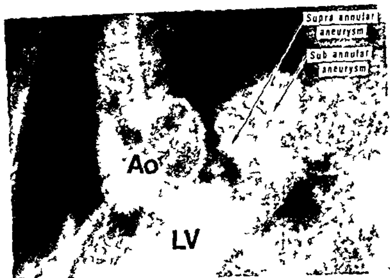


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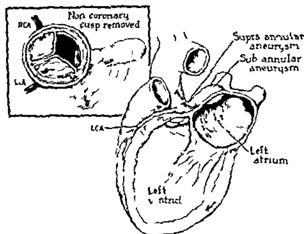


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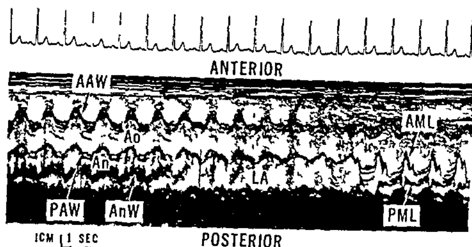


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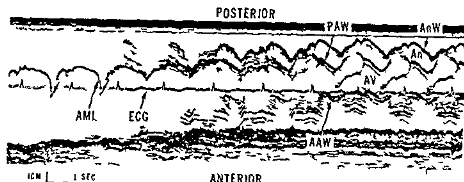


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Ventricular pre excitation and prolonged Q-T interval syndromes in a patient with mitral valve prolapse

David M Mirvis, M D
Stanley W Erwin M D
Memphis Tenn

Mitral valve prolapse has become a commonly recognized clinical syndrome [1] [2] characterized by typical auscultatory echocardiographic and ventriculographic abnormalities Clinical manifestations are varied ranging from the asymptomatic state to premature and sudden death

The occurrence of supraventricular and ventricular dysrhythmias has received wide attention because of their frequency being recorded in as many as 75 per cent of subjects during exercise [3] and because of their presumed relationship to the lethal potential of the syndrome [2] Little however is known of their pathogenesis In the case to be described mitral valve prolapse was associated with two other clinical syndromes known to predispose to cardiac dysrhythmias

Case report

A 34 year old black woman was referred for evaluation of palpitations and chest pain The pain was anginal in quality and always followed the onset of rapid regular palpitations lasting one to five minutes She denied dizziness or syncope Past history revealed no risk factors for ischemic heart disease and no history of rheumatic fever She was taking no medications The patient had two sisters one with and one without palpitations and a heart murmur

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This investig tion was supported in part by a Debo ah Hospital Foundati n Research Grant and by Un ted States Public He lth Service Grant HL-°°69 from the National He rt, Lung nd Blood Inst tute Nat nal Institutes of H alth

Received for publicati n Sept 21 197"

Accepted for publ at n Oct 10 1977

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Physical examination revealed normal vital signs She had a straight back and a pectus excavatum A mid systolic click followed by a Grade III/VI high frequency murmur was heard at the cardiac apex A straight back and narrow A P chest diameter were observed on x ray An echocardiogram was typical of mid late systolic prolapse of the posterior mitral valve leaflet

Electrocardiographic findings (Fig 1) included a sinus rhythm (77 beats per minute) a PR interval of 120 msec., a normal QRS complex without a delta wave diffuse ST T abnormalities and a prolonged Q T interval (5?0 msec Q T = 0 58) Mean QRS axis was 10 degrees Precordial voltage exceeded criteria for left ventricular hypertrophy A 24 hour ECG tape recording revealed frequent episodes of ventricular bigeminy and three runs of unsustained ventricular tachycardia 8 to 10 beats in duration Serial electrocardiograms demonstrated lability of the Q T interval measuring 0 42 to 0 60 msec during the study period

Serum electrolyte concentrations (Na K Cl HCO Ca Mg) blood cell counts and renal and hepatic function tests were normal. An audiogram was likewise normal

Electrophysiologic studies were performed in an unpremedicated postabsorptive state after obtaining voluntary informed consent Two bipolar electrode catheters were advanced to the high right atrium and His bundle areas from the right femoral vein Intracardiac electrocardiograms were recorded during sinus rhythm and during atrial pacing after bandpass (50 to 400 Hz) filtering His bundle recording was validated by His bundle pacing

During sinus rhythm (cycle length = 1060 msec Fig 2A) values for P A A H and H V intervals were 30 30 and 40 msec respectively The Q T interval was normal at the time of study Body surface and His bundle electrocardiograms and interval measurements during incremental atrial pacing are presented in Figs 2B through 2F Reducing the cycle length from 960 msec. to 560 msec resulted in a minimal (< 10 msec) increase in A H intervals Further decrements in pacing cycle length to 450 msec produced no further changes in A V nodal conduction time At this heart rate the patient experienced chest discomfort similar to that causing referral Tachyarrhythmias were not induced during the procedure

Left ventriculography in the right anterior oblique projec

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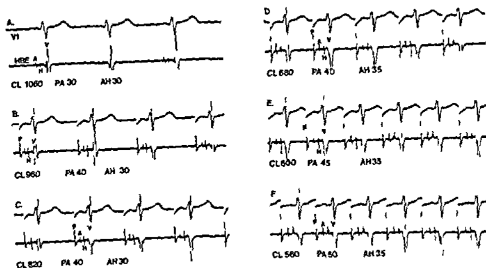


Fig 2 Electrocardiograms recorded from precordial Lead V and bipolar intracardiac lead at the His bundle recording area *(HBE)* during sinus rhythm *(panel A)* and during atrial pacing *(panels B through F)* P A H and V refer to deflections generated by high right atrial tissue *(panel A)* or by the artificial pacemaker *(panels B through F)* the low right atrium the His bundle and the ventricular muscle respectively Identified in each panel are cardiac cycle length *(CL)* and PA and AH intervals in msec

Chandra and co workers[1] Chandraratna and collaborators [4] and by Bjerregaard and associates[19] In contrast to the number of reports of classical Wolff Parkinson White patterns A V nodal bypass of the type described here has been described in but three patients referred to by Devereux and colleagues and by Kastor and Josephson[20] Finally Krikler and co workers[21] reported one case of mitral prolapse with the Mahaim fiber type of pre excitation

Overlap syndromes such as described here and in the reports previously referred to may be considered as coincidental concurrences of abnormalities without special significance This approach is particularly justified when one disorder is common, as in mitral valve prolapse An alternative approach is that the overlaps signify that one lesion predisposes to the others in some undefined manner The over all clinical spectrum of the commonest disorder i e mitral valve prolapse depends then upon the frequency of concurrence with other lesions For example the incidence of clinically significant dysrhythmias in subjects with prolapse may relate to the incidence of anomalous atrioventricular pathways of prolonged Q T intervals or of other definable electrophysiologic aberrations in these patients This was suggested by Shappell and associates [4] with regard to Q T intervals Kastor and Josephson[20] provided support for this concept by demonstrating bypass tracts in all studied patients with prolapse suffering with supraventricular tachycardias It may therefore be possible to subdivide all patients into subgroups with different risks of morbidity and mortality

Summary

A 34 year old woman with mitral valve prolapse frequent ventricular dysrhythmias and chest pain was studied Surface electrocardiograms demonstrated short PR and prolonged Q T intervals A V nodal conduction times during atrial pacing were characteristic of A V nodal bypass tract function The case is thus interpreted to be one of overlap between three syndromes known to predispose to cardiac dysrhythmias i e mitral valve prolapse Lown Ganong Levine syndrome and prolonged Q T interval syndrome

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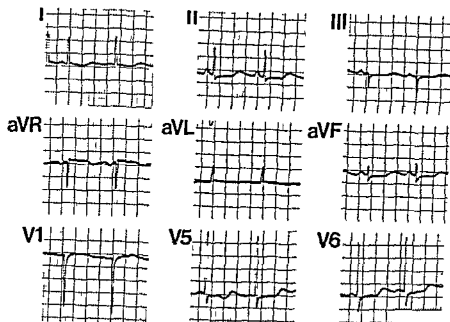


Fig 1 Electrocardiographic records demonstrating a short P R interval (0 12 sec) diffuse ST T abnormalities and a prolonged Q T interval

tion confirmed the presence of posterior mitral leaflet prolapse Coronary angiograms were normal

Both sisters were subsequently examined One with a history of palpitations had a mid systolic click electrocardio gram demonstrated a PR interval of 100 msec and a Q T interval of 0 54 msec The second sister was asymptomatic with normal physical findings and electrocardiogram Other family members were not available for evaluation none had cardiac symptoms

Discussion

Three distinct diagnoses are apparent in this patient First she had the typical historical physical, auscultatory echocardiographic and ventriculographic features of mitral valve pro lapse [1 3 6] Of particular relevance here is this patient s history of palpitations, correlating with episodic ventricular bigeminy and tachycardia on dynamic electrocardiography Such rhythm disturbances may be observed in up to three fourths of afflicted persons and may be pathogen ically related to abnormal stretching of papillary muscles[1] or of pacemaker like fibers in the mitral leaflets [7]

Secondly, *ventricular pre excitation of the* form described by Lown Ganong and Levine[8] is documented by the short PR and A H intervals at rest, the failure of A V nodal conduction to slow at increased heart rates the normal H V time and the absence of a delta wave [9 10] This electrophysiologic anomaly is correlated with the presence of a path extending from the atrium to the His Purkinje system, bypassing the slowly conducting A V node The relationship between this syndrome and cardiac dysrhythmias is well known [8]

Lastly, the prolonged Q T interval conforms to another electrophysiologic anomaly clearly asso ciated with *cardiac dysrhythmias* [11 13] This syn drome which may be familial with or without deafness or related to drug therapy[12] has been associated with autonomic dysfunction Sudden death and syncope are caused by ventricular fibrillation or asystole

Thus this patient represents an overlap of three conditions—one common and two uncom mon—predisposing to cardiac dysrhythmias Sim ilar cases of two concurrent abnormalities are well known Prolonged Q T intervals in patients with mitral valve prolapse not related to drug therapy have been noted in five of 24 patients reported by Gooch and colleagues[3] but in only one of 144 subjects reviewed by Barlow and Pocock [1] The possible critical role of this finding in causing sudden death in patients with prolapse has been considered by Shappell and asso ciates [14]

Likewise various forms of ventricular pre exci tation have been occasionally noted with mitral leaflet prolapse Gallagher and co workers[15] reported seven patients with prolapse and typical Wolff Parkinson White syndrome suggesting a greater incidence than expected by chance alone Other similar cases have been described by Fujino and associates [16] by Devereux and colleagues [2]

Fatigue dyspnea and abdominal swelling in a 13 year-old boy

Noble Fowler M D *
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B C CHMC No 228488 was a healthy active 13 year old boy prior to insidious appearance of fatigue and listlessness poor appetite failure to gain weight and eventually dyspnea on excretion over an 8 month period Most recently mild abdominal swelling had been noted and his parents had observed mild perioral cyanosis following moderate exercise Two older brothers and a sister were in good health There was no history of fever chest pain peripheral edema gastrointestinal disturbance arthralgia or of exposure to tuberculosis

Physical examination on admission revealed a somewhat edematous boy with moderate abdominal distention and pitting ankle edema who was acyanotic at rest and in no acute distress Weight was 97 pounds temperature 98 F respirations 34/minute pulse 100/minute and blood pressure 90/70 mm Hg without pulsus paradoxicus Femoral artery pulsations were felt but intensity was not recorded The jugular veins were distended to 10 cm above the clavicle while he was seated there was no Kussmaul sign Rales were present over both posterior lung fields Heart size was within normal limits by palpation and no thrill was evident S was normal S was loud and closely split with an increased pulmonic component A Grade II/VI pansystolic murmur was heard at the apex An abdominal fluid wave was demonstrated and the liver edge was palpated 8 cm below the right costal margin No neurological or musculo skeletal abnormalities were observed

Laboratory data disclosed a hemoglobin of 14 8 Gm /dl The white blood count was 5400/mm³ with 74 per cent polymorphonuclear cells 13 per cent lymphocytes 11 per cent monocytes and 2 per cent eosinophils Platelets were normal in number and appearance Urinalysis was normal The blood urea nitrogen was 16 mg /dl and serum concentration of Na K Cl and bicarbonate were normal

The electrocardiogram showed sinus rhythm with broad notched P waves The ST segments were depressed and the T waves flat in Leads 1 2 3 aV$_F$ V$_5$ and V$_6$ Voltage was high normal and criteria for ventricular enlargement were absent

He was treated with digoxin and chlorothiazide and his weight fell 15 pounds over a three day period Hepatomegaly and neck vein distention regressed but did not disappear

Cardiac catheterization performed 2 weeks after admission revealed the findings shown in Table I

Cineangiocardiography showed no intracardiac shunts both ventricles were normal sized and contracted well Prominent left atrial dilatation

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Received for publication N 1 1977

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history of heart disease The patient when first seen at age 13¼ had symptoms of heart failure namely tachycardia tachypnea and low blood pressure even for this age No evidence of paradoxical pulse was described His venous pressure was quite high There were rales over both lung fields but his heart was not thought to be enlarged There was a systolic murmur at the apex that sounded as if it might be indicative of mitral incompetence No diastolic murmur was heard A gallop rhythm was not heard at this time We do not know whether or not there was a sharp Y descent of the cervical venous pulse

The original suspicion of constrictive pericarditis was raised I am sure because of his persistent circulatory difficulty and his relatively normal heart size on roentgenogram and perhaps inconspicuous pulmonary congestion The patient was treated for heart failure and had a response with diuresis It would be interesting to know what happened to the venous pressure at that time If he had constrictive pericarditis one would not expect any great improvement If he had congestive heart failure secondary to valvular or myocardial disease one might have expected a fall in venous pressure with clinical improvement

The patient then underwent cardiac catheterization that showed a number of things of interest including a rather low content of oxygen in his vena cava and right atrium suggesting that he may have had a subtle decrease in his cardiac output despite the low normal cardiac index His left ventricular end diastolic pressure was 25 which is quite elevated and was about the same in the pulmonary artery and only slightly greater than that in the right atrium Atrial pressures were almost equal The pressures measured are of the kind seen in constrictive pericarditis or cardiac tamponade but may also be seen occasionally in cardiomyopathy

A cineangiogram showed a large left atrium and no intracardiac shunt Lack of both a diastolic murmur and of a diastolic pressure gradient between the left atrium and left ventricle indicates that mitral stenosis was not the cause of left atrial enlargement We are uncertain as to whether there was or was not mitral incompetence LV contractility was normal an important finding in a patient with this degree of circulatory difficulty because it indicates that the site of the

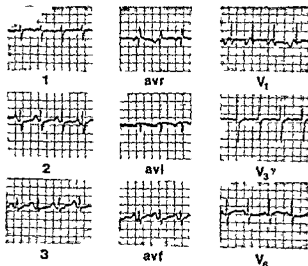


Fig 1 Electrocardiogram from 15-year old male patient obtained 2? months after onset and 4 weeks prior to death

impedement was proximal to the body of the left ventricle

Thus we have a young lad with circulatory failure and certain features suggesting that he had constrictive pericarditis namely a relatively small heart elevated venous pressure elevation of diastolic ventricular pressures and atrial pressure equalization The relatively normal cardiac output is more in keeping with pericarditis than cardiomyopathy or some other cardiac disorder

There has been considerable interest especially in recent years in the problem of restrictive cardiomyopathy a rare disorder of the myocardium in which the heart is not greatly dilated in which the venous pressure may remain elevated and which has certain features in common with constrictive pericarditis I would like now to concentrate on the differential diagnosis between these two disorders Distinction between them is very important because constrictive pericarditis is a potentially curable illness whereas restrictive cardiomyopathy may be helped by digitalis and diuretics but a cure is unlikely to be achieved

The failure of systemic venous pressure to decrease following treatment is an important characteristic of constrictive pericarditis but may also be seen in restrictive cardiomyopathy The venous pressure must have been high after clinical improvement in this case because at cardiac catheterization right atrial pressure was elevated Patients with restrictive cardiomyopathy may also have pulsus paradoxicus limiting its

Table I Catheterization data

Position	*% O_2 saturation*	*Pressure (mm Hg)*	*Mean*
SVC	64		
RA high	60		
RA mid	65	A = 18 V = 17	16
RA low	67		
LA	96	A = 22 V = 20	18
LA		A = 20 C = 16	18
LPV	94	A = 26 V = 20	19
RV	72	45/20	
MPA	73	50/25	32
LPA	73	48/24	
LPA MPA RV RA		48/24 45/22	
RA mid	66		
LV	95	88/25	
LV		95/25	
LA			22
LV AO		95/25 95/70	80
Ejection fraction = 53%			
Cardiac index = 3 3/min /M²			

was demonstrated Mitral insufficiency was not demonstrated but the study was not adequate for this purpose

One week later exploratory mediastinotomy was performed through a median sternotomy incision The parietal pericardium was described as slightly thick and hypervascularized The pericardial sac was the seat of filmy fibrous adhesions that were easily broken by blunt dissection The surgeon s finger easily probed the entire sac and no evidence for constriction was found The epicardial surface of the myocardium was an abnormal pale yellow color

Examination of the 2 cm square piece of parietal pericardium that was removed showed mild diffuse collagenous thickening without evidence of active inflammation or repair No granulomas or mineral deposits were identified The lesion was interpreted as consistent with a remote pericarditis of unknown type

Lacking evidence for constrictive pericarditis the patient was thought to have a restrictive cardiomyopathy He was discharged following an uneventful postoperative recovery on digoxin, 0 125 mgm twice a day, furosemide 40 mg three times a day spironolactone 12 5 mg three times a day and supplemental KCl

His subsequent activity was limited by increasing dyspnea and orthopnea On second admission to the hospital 14 months later he was unable to walk more than 20 yards without resting Pitting peripheral edema, jugular venous distention and hepatomegaly were again prominent Tachycardia, cyanosis of the lips and acrocyanosis were present at rest Peripheral pulses were weak Clinical signs of cardiomegaly were still absent S_2 was split An S_4 gallop rhythm became audible and a holosystolic murmur persisted at the apex. Phonocardiography demonstrated a prominent mid systolic click suggesting mitral valve prolapse The scalar electrocardiogram (Fig 1) was unchanged except for right axis deviation The vectorcardiogram in comparison to the initial tracing, showed a change from counterclockwise to clockwise inscription in the horizontal plane indicating right ventricular hypertrophy He responded to intravenous administration of ethacrynic acid with a 9 pound weight loss to 78 pounds but fluid rapidly re accumulated After a brief final admission several weeks later, he died suddenly during a similar therapeutic endeavor

Discussion

DR FOWLER This patient represents a problem of the differential diagnosis of heart disease with systemic and probably pulmonary congestion occurring over a period of 2½ years beginning at the age of 13½ and terminating in death apparently from circulatory failure 1½ years later Of importance is the fact that there was no family

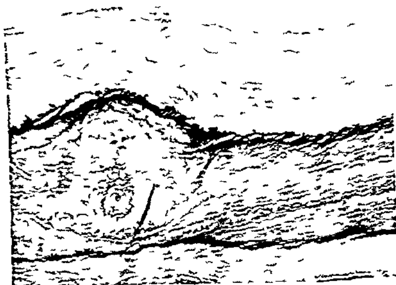


Fig 4 Hyalinized mineralized epicardium lacks cellular infiltrate (Hematoxylin and eosin original magnification ×125)

myocardial disease over pericardial disease Another point we might make about the plain roentgenogram is that if the patient has a combination of thickening due to scar plus fluid between the pericardial layers the pericardial silhouette may be quite sizeable Calcification of the pericardium is not diagnostic of constriction and it is found in only 50 per cent of patients with constrictive pericarditis So with signs of constriction the size of the cardiac silhouette may be normal or it may be considerably enlarged by scar alone or scar in combination with fluid Pericardial fluid predominates in the effusive-constrictive pericarditis that may simulate congestive heart failure in adults May we see the x rays

DR. DUNBAR The heart at the time of the first admission was minimally enlarged but was interpreted as showing striking enlargement of the left atrium (Fig 2) The lungs show some congestion with multiple Kerley lines which are rather nonspecific Bilateral pleural fluid and thickening is present at least to a moderate degree Despite its near normal size there is a striking abnormality of cardiac contour with straightening of the left heart border I do not recognize any pericardial calcification although in fairness I should add that at least one staff radiologist suspected its presence

The films obtained late in the course of his disease show little change

DR FOWLER I am very struck by the very large left atrium although it did not look so striking on the barium esophagogram The pronounced isolated chamber enlargement would be unusual to say the least in a patient with constrictive pericarditis as the constrictive process is usually rather uniformly applied although there may be some sparing of the pericardium of the posterior left atrial wall The second thing I would emphasize is that Dr Dunbar has mentioned the presence of Kerley lines These are usually equated with elevation of pulmonary lymphatic and venous pressure and although occasionally seen with constrictive pericarditis are much more common in congestive heart failure Therefore we have two radiograph features which are against constrictive pericarditis and favor primary myocardial disease and two points relatively normal cardiac size and equivocal evidence of pericardial calcification which are in keeping with constrictive pericarditis

In the electrocardiogram we find several points of interest In the initial tracing the P waves are very prominent and late peaks suggest that this is due to left rather than right atrial involvement The ST segments are abnormal and may reflect digitalis therapy or may indicate some other diffuse myocardial problem The voltage is a bit high but at this age this is difficult to judge It might reflect some left ventricular involvement The delay in the left precordial R wave might



Fig 2 Chest roentgenogram and barium esophagogram performed at the time of the first admission



Fig 3 Left anterolateral surface of parchment heart Unusual quality of epicardium is highlighted by unusual wrinkles and folds that have been augmented by development of a tissue plane between the outer hyalinized zone and less altered epicardium adjacent to the myocardium Path of most heavy mineral deposit traverses field above line of arrows and corresponds roughly to the plane of the mitral valve ring *(dashed line)*

usefulness as a discriminating feature The patient had a negative Kussmaul sign that is, absence of inspiratory collapse of neck veins We haven't found that to be helpful, for it may be present in patients with heart failure of any cause and absent in constrictive pericarditis

Precordial phonocardiography is helpful if it shows the 'knock sound which is a sharp sound that usually occurs 06 to 12 sec after the second heart sound in patients with constrictive pericarditis It sounds very much like a mitral opening snap but is not followed by a diastolic murmur It is a bit earlier than the gallop rhythm which usually occurs about 14 sec after the second heart sound The phonocardiogram obtained on the first admission in this patient showed neither a knock nor a gallop The absence of the knock in this boy does not at all rule out pericardial disease but the subsequent development of a late sound consistent with a gallop would be a point against pericardial disease

I shouldn t omit the fact that precordial palpation is also important If one feels a good active precordium and can feel the gallop impulse it is unlikely that one is dealing with significant pericardial disease

A few words about the chest roentgenogram In patients with constrictive pericarditis the heart size may be almost normal and the lungs are usually clear Typically there is no congestion in the lungs and rales are not heard The presence of rales in a patient such as this one would favor



Fig 7 *A* Atrophic basilar myocardium adjacent to the mitral valve consists of shrunken fibers separated by myxoid ground substance (Hematoxylin and eosin original magnification ×300) *B* Small muscular pulmonary artery exhibiting intimal and medial infiltrate of polymorphonuclear and mononuclear cells including stimulated lymphoid cells (Hematoxylin and eosin original magnification ×500)

constrictive pericarditis The echocardiogram may also be helpful in terms of what it tells us about ventricular size and function and mitral valve performance Dr Meyer would you please interpret the echocardiogram for us

Dr Meyer This tracing was made in September 1973 The posterior leaflet of the mitral valve instead of a normal gradual movement toward the anterior chest wall during systole moves somewhat posteriorly and there is evidence of pan prolapse of this valve into the left atrium I would also point out the marked increase of his left atrial dimension The left ventricular cavity dimensions are normal. The septal and free wall motions are normal and the calculated ejection fraction is in the low normal range The pericardium is difficult to assess but there is no fluid in the pericardial space The later echocardiograms show all of these features to be persistent Right ventricular enlargement was not detected

Dr. Fowler Do you think the echocardiogram can be used to exclude the necessity for surgical exploration for constrictive pericarditis?

Dr Meyer No The echocardiogram may be useful in identifying an effusion but it is not useful for the determination of constriction In a negative sense the absence of any demonstrable sign of cardiomyopathy would make exploration of this patient mandatory

Dr. Fowler Do you think that he had mitral insufficiency due to his prolapse?

Dr Meyer Yes However the failure of the left ventricle to dilate commensurately with the left atrium is puzzling

Dr Fowler We are left without a definitive angiogram and thus are not certain about mitral insufficiency Clearly however this patient s heart had more trouble filling than emptying He had both auscultatory and echocardiographic evidence favoring a diagnosis of mitral insufficiency and this must have contributed to the left atrial enlargement From the surgical exploration we are told that he did not have significant pericardial disease although he did have some evidence of pre-existent inflammation

I believe that the pattern of abnormality in this patient fits more with restrictive cardiomyopathy than with constrictive pericarditis This is much



Fig 5 Basilar left ventricle Mineralized epicardial scar in A V groove extends into the myocardium pale myocardium *(arrows)* exhibits severe atrophy Mitral valve part of posterior papillary muscle and remainder of myocardium are unaltered (Hematoxylin and eosin original magnification ×4)



Fig 6 Focal prolapse *(arrows)* and mild diffuse thickening of mitral valve leaflets are inconspicuous Papillary muscles are normal The large left atrial chamber dwarfs the normal sized left ventricle

suggest a delay in left ventricular activation His later electrocardiogram is more striking on two of these points (Fig 1) He had developed an impressive degree of right axis deviation of about 120 degrees His P waves are larger yet with the same late peak and in V_1 he has a prominent secondary negative component of the P wave which is usually equated with left atrial activation and is in keeping with the left atrial enlargement seen on the roentgenogram In addition, he now has a very prominent R wave suggestive of right ventricular enlargement or conduction delay His S waves have become more prominent over the left precordium which would also be in keeping with right ventricular enlargement In an adult with this kind of electrocardiogram one would think strongly about the possibility of mitral valve disease particularly obstruction at the mitral valve orifice

In a typical case of pericarditis one would expect to see sinus rhythm low voltage of QRS complexes in the limb leads and normal P waves A left atrial enlargement pattern may sometimes be seen but one would not expect the ventricular abnormalities suggested by the electrocardiogram in this patient About 25 per cent of the patients show atrial fibrillation The demonstration of a pattern of bundle branch block or of ventricular hypertrophy is a strong point against constrictive pericarditis Of course a patient may always have two diseases

What does one do with such a patient whose hemodynamic studies show presures consistent with constrictive pericarditis but in whom there are many data that are inconsistent with this diagnosis A left ventricular angiogram may be helpful in defining the thickness of the wall of the ventricle and of the overlying pericardial tissue However the angiogram is not always helpful in defining wall thickness as has been our experience in two of seven cases with other evidence of

of the viscera included early congestive cirrhosis

In the absence of infiltrative or reparative lesions of the endocardium or subendocardial myocardium I believe a diagnosis of restrictive cardiomyopathy is untenable The absence of histopathological changes in the papillary muscles makes it unlikely that dysfunction of these structures was responsible for the auscultatory signs of mitral insufficiency Although the left atrium was markedly dilated dilatation of the mitral valve ring was not a feature and moreover has been recently discredited as a major cause of regurgitation The functional consequences of restriction of movement of the mitral valve apparatus by epicardial scar and basilar myocardial atrophy are not simple to predict but mild diffuse thickening of the leaflets and focal prolapse help to substantiate the clinical evidence that mitral valve dysfunction existed

Constrictive pericarditis due primarily to epicardial scarring as occurred in this case is extremely unusual and appears not to have been previously well documented Annular constriction has been described at the base of the heart in the region of the A V groove or in relation to the great arteries or veins * It may calcify and has been reported to cause discrete intra or extracardiac obstruction by producing rigidity of the valve or vessel which it encircles Annular constriction has not been reported in pericarditis due to tuberculosis or collagen-vascular disease and thus one may speculate that epicarditis due to virus or bacteria is the precursor in our patient

ANATOMIC DIAGNOSES Constrictive epicarditis idiopathic—calcification left A V groove—focal myocardial atrophy adjacent to mitral valve ring—minor prolapse of mitral valve Left atrial dilatation Right ventricular hypertrophy Fresh and organized pulmonary emboli Necrotizing vasculitis, lungs acute Chronic passive congestion all viscera Congestive cirrhosis early Fibrosing pleuritis peritonitis perisplenitis

DR FOWLER I have several comments I have read in the older literature of patients with constricting bands in the AV groove and even sometimes with diastolic murmur presumably due to mitral stenosis Only one such case was reported in 53 patients with constrictive pericarditis but a separate report described three patients with features in common with this case These features were primarily constriction of the left ventricle a constricting band in the A V groove producing mitral stenosis and left atrial and right ventricular enlargement There seems to be no doubt that he did have significant epicardial scar Having been in a situation before where the surgeon has not recognized constrictive pericarditis I am a little dismayed that the biopsy sample included only parietal pericardium and I wonder why there wasn t an epicardial and myocardial biopsy obtained It probably would have been very helpful

Do you think that his epicardium looked like this when he was operated upon? It seems to me that since the surgeon was unimpressed by it that this may have been a later development Was the epicarditis diffuse and do you think that the epicardial scar could have been removed and the process of constriction relieved?

Despite the surprising amount of pericardial disease I wonder still if there wasn t some myocardial factor in this boy s progressive disease

DR BOYE There may have been progressive epicardial scarring during the 16 month interval between exploration and death but I believe that the basic process was established prior to biopsy the surgeon reported an abnormal yellowish appearance of the epicardial surface but did not appreciate its significance its appearance remained deceptively benign 1½ years later at autopsy The only myocardial lesion was a very limited one at the base of the heart adjacent to the mitral A V groove Of course one cannot *absolutely* eliminate a coexistent functional myocardial disorder solely on the basis of histologically normal myocardium

The diffuse epicardial scar in my opinion might have been stripped without doing serious damage to the myocardium but I think that some difficulty might have been encountered in removing the scar in the left A V groove where it was heavily calcified and penetrated the basilar myocardium Annular constrictive pericarditis has been reported to be amenable to surgical correction if it is recognized

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the rarest of the forms of primary cardiomyopathy, the two more common forms being the congestive and obstructive types What is the nature and etiology of this condition? Restrictive cardiomyopathy is defined as a state "resembling constrictive pericarditis with diastolic filling difficulty due to myocardial rigidity, infiltration and often with endocardial involvement "[2] The more commonly encountered variants are due to amyloidosis localized endomyocardial fibrosis (East Africa), scleroderma, neoplasm, and hemochromatosis[3] Many cases are idiopathic Because this patient lacks stigmata of any of these associated conditions and is so young I must place his disease in the idiopathic category

Patients who have a viral infection may have mild pericarditis and myocarditis and then go on to develop a picture of cardiomyopathy though usually of the congestive type Conceivably there could be post inflammatory endomyocardial sclerosis restricting left ventricular expansion and causing dysfunction of papillary muscles leading to mitral prolapse Thus I would speculate that in this case a restrictive cardiomyopathy may have begun with a viral illness

CLINICAL DIAGNOSIS Restrictive cardiomyopathy idiopathic—secondary mitral prolapse and left atrial dilatation

DR BOVE The outstanding feature at autopsy was a florid fibrous tissue proliferation that involved much of the surface of both pleural cavities the peritoneum and to a lesser extent the parietal pericardium We considered that this might be the result of infection or systemic collagen-vascular disease but could find evidence for neither Therefore we interpreted the fibrosis of serosal surfaces as a concomitant of chronic effusion in a boy with systemic venous hypertension

The nature of the cardiac disorder at first eluded us as it had eluded the surgeon and the cardiologist The prosector easily had separated the parietal pericardium from the heart and it was only moderately increased in thickness Doubting that either parietal pericardial constriction or cardiomyopathy was the basic problem, we turned our attention to the epicardium which was diffusely opacified wrinkled and parchment like in texture (Fig 3) Microscopically the superficial epicardium of both ventricles was replaced by a peculiar almost acellular focally mineralized hyalin scar of uniform thickness (Fig 4) that had partially separated from the underlying left ventricular myocardium Atrial epicardium was minimally altered The tough non elastic, hyalinized epicardium though it was deceptively thin, appeared capable of restricting left ventricular motion, particularly its expansion during diastole Further examination revealed additional foci of dense calcified partially ossified scar in the left and posterior atrioventricular groove that appeared to have immobilized the mitral valve ring and focally extended into the subjacent basilar myocardium causing local atrophy (Fig 5) We concluded that rigid epimyocardial scar constituted the basis for markedly impaired filling of the left ventricle

Cardiac weight of 220 Gm was not abnormal for a 14 year old boy 67 inches tall Both atria were dilated, the left atrium markedly so and there was mild dilatation and hypertrophy of the right ventricle The configuration of the left ventricular chamber was slightly more spherical than normal but the wall did not appear hypertrophied The pulmonary valve circumference was normal but the aortic valve circumference was smaller than expected 4 8 cm /5 9 cm, perhaps reflecting reduced flow The only other valvular change consisted of mild gelatinous thickening of the mitral leaflets with minimal prolapse at the junction of the anterior and posterior leaflets (Fig 6) Endocardial fibrosis or mural thrombi were not a feature The mitral papillary muscles exhibited normal bulk, were not malpositioned and were composed of unaltered fibers

Histological evidence for myocardial hypertrophy was present in sections from the right ventricle, but absent in the left ventricle Neither inflammation nor fibrosis were detected in six samples of the LV myocardium

The lungs showed severe chronic passive congestion several fresh pulmonary thromboemboli and microscopical evidence of fibroocclusive vascular disease consistent with previous episodes of embolization There were multiple small hemorrhagic infarcts several of which were the result, not of thromboemboli but of acute necrotizing arteritis (Fig 7) The latter is a recognized but uncommon complication of sustained pulmonary hypertension and has been noted to occur with particular frequency in patients with severe mitral stenosis Severe chronic passive congestion

Echocardiography in ischemic heart disease
Present status and future prospectives

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The utility of ultrasound in a wide variety of pericardial myocardial valvular and congenital heart diseases has been repeatedly demonstrated but its role in the evaluation of patients with coronary artery disease remains unsettled With the growing popularity of surgical therapy for coronary disease and the recent interest in the modification of infarct size there is an increasing need for a noninvasive method of evaluating candidates for these interventions and assessing their results

Echocardiography also appears to be at an important juncture in its evolution M mode echocardiography has progressed from an investigational technique to a routine clinical study However rapid advances in instrumentation have made systems capable of two dimensional real time visualization of the heart increasingly available Consequently much of the current research in cardiac ultrasound involves cross sectional echocardiography and preliminary findings suggest that this technique will result in a wider range of applications particularly in patients with coronary artery disease

It therefore seems appropriate at this time to critically assess the literature relating to the use of ultrasound in the setting of ischemic heart disease and to comment upon present approaches and future potential applications

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This work was supported in p rt by NHLBI Pr gram Project Gra t HL 06285

Received f r publ t n Ja 24 19 8

Reprint req ests B rry Massı M D Cardı ascular Divisı n M ffitt Hospital, Room 1186 Uni ersity f C lif rnia San F n isco C lif 94143

000 8 03/78/100543 + 0.$00 0/0 © 19 8 The C V Mosby Co

Measurements of left ventricular volume and function

The application of ultrasound to the measurement of left ventricular volume and contractile performance gained considerable attention in the period between 1970 and 1973 Initially the movement of the mitral valve ring and the left ventricular posterior wall were examined and utilized as indices of stroke volume and contractile function[1,2] Subsequently a number of investigators found good correlations between echographic and angiographic volume and ejection fraction determinations Two methods have been employed to calculate these parameters Most workers have assumed that the left ventricle can be geometrically approximated by a prolate ellipse model with two equal short axes (d and d_2) and a long axis (l) which is twice the length of the short axis[3-6] The volume (V) of such an ellipse is given by the formula

$$V = \frac{\pi}{6} d d l$$

Using this model and further assuming that the echographic left ventricular internal dimension (LVID) approximates the short axis left ventricular volume can be determined from the formula

$$V = \frac{\pi}{3} LVID^3$$

or simply approximated as

$$V = LVID^3$$

Other investigators have determined left ventricular volume from linear regression relationships between angiographic volume and echographic left ventricular internal dimension[8,9] Echographic measurements of the mean velocity of circumferential fiber shortening [1] and systolic

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Echocardiography in ischemic heart disease
Present status and future prospectives

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The utility of ultrasound in a wide variety of pericardial myocardial valvular and congenital heart diseases has been repeatedly demonstrated but its role in the evaluation of patients with coronary artery disease remains unsettled With the growing popularity of surgical therapy for coronary disease and the recent interest in the modification of infarct size there is an increasing need for a noninvasive method of evaluating candidates for these interventions and assessing their results

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This work was supported in part by NHLBI Program Project Grant HL 06285

Recei ed f publicatio J n 24 1978

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0002-8 03/78/100543 + 0 $00 0/0 © 1978 The C V Mosby Co

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Other investigators have determined left ventric ular volume from linear regression relationships between angiographic volume and echographic left ventricular internal dimension [8] Echo graphic measurements of the mean velocity of circumferential fiber shortening[10] [1] and systolic

time intervals[1-13] have also been found to correlate well with those from ventriculograms and carotid pulse tracings, respectively

However, these studies utilized few if any, patients with coronary artery disease In fact obvious exceptions to the over all correlations were found in patients with asynergy[6 8 10 11] Early experimental studies documented focal changes in the echographic pattern of wall motion with induced segmental ischemia,[14 16] raising doubts about the reliability of ultrasonic determinations of volume and ejection fraction based upon measurements derived from a single plane through the heart In addition serious questions were raised about the validity of the prolate ellipse model and the assumed 2 1 ratio of the major to minor axes in patients with enlarged and asymmetric ventricles Clinical studies soon appeared which clearly confirmed these suspicions,[17 18 20] demonstrating poor correlation between ultrasonic and angiographic measurements in patients with asynergy

Thus, the initial enthusiasm for quantitative echographic measurements of ventricular volume and function has yielded to skepticism Nonetheless several authors have at least partially disassociated themselves from this consensus Ratshin and associates[1] suggested that the end diastolic dimension and end diastolic volume determinations remain accurate even in the presence of asynergy although systolic parameters and therefore ejection fraction do not Ludbrook and colleagues[2] found that echographic and angiographic measurements of the mean velocity of circumferential fiber shortening also continued to correlate well but this finding has been disputed[23]

Recently Massie and co workers[24] reported a new index of ventricular function based upon a simple measurement of the minimum separation between the mitral valve at its E point and the most posterior excursion of the interventricular septum Normal subjects and those with preserved ventricular function have little (< 5 mm) or no mitral-septal separation while those with reduced ejection fraction have increased separation Their results indicate that E point septal separation is also a reliable index of ventricular function in patients with coronary artery disease correlating well with biplane angiographic ejection fraction ($r = -.86$ $p < 001$) and remaining significantly more accurate than other echographic indices in these patients

Currently, it appears that echographic measurements of left ventricular size and function in patients with coronary artery disease may provide helpful qualitative information, but are not accurate enough for quantitative investigation In particular, most studies indicate that patients with depressed left ventricular function by echocardiography will also have abnormalities in invasive indices, but that patients may appear to have normal function by ultrasound and still have significant dysfunction by angiographic measurements

Evaluation of wall motion

Segmental wall motion disturbances are the hallmark of both acute and chronic ischemic heart disease[5 26] Several animal studies have shown that the echocardiogram will demonstrate decreased amplitude and velocity of wall motion and diminished wall thickening in regions of experimentally produced infarction or ischemia[13 15 27] Compensatory increases in wall motion may be detected in uninvolved regions[27]

Jacobs and associates[25] have actively investigated the clinical use of echocardiography to detect segmental wall motion disturbances Initially utilizing the standard left parasternal echographic window from which the anterior interventricular septum and the true posterior wall can be visualized they were able to detect abnormalities in 75 per cent of patients with angiographically demonstrated asynergy Subsequently, they advocated expanding the usual window to the subxiphoid area and laterally along one or more intercostal spaces[9 30] Addition of these approaches increased their number of successful examinations and allowed visualization of more extensive areas of the left ventricle including the mid third of the interventricular septum and the posterolateral and anterior walls[31] Even though the involved area might be missed, compensatory hyperactivity of another region could frequently be detected

Such techniques have made it possible for two groups to detect decreased wall motion corresponding to the location of electrocardiographic Q waves in 100 per cent and 84 per cent, respectively of patients with acute transmural myocardial infarction[32 33] and often to detect other areas of compensatory hypercontractility[33 34] Recent

ly investigators have evaluated the degree of segmental wall thickening during systole in addition to wall motion Experimental studies have indicated that thickening is reduced by infarction and ischemia[27] In patients with acute myocardial infarction actual systolic wall thinning can be seen[35] Measurement of wall thickening allows assessment of regional function particularly of the interventricular septum in the presence of conditions which nonspecifically affect its motion such as right ventricular volume overload and electrical conduction disturbances

Echographically visualized segmental abnormalities have also been found in areas of old infarction and in the distribution of critically narrowed coronary arteries[2, 30] In particular disorders of septal motion have been found in some but not all patients with severe proximal left anterior descending coronary artery lesions[3, 3] A more quantitative estimation of the over all amount of asynergy has also been developed using a regression formula from which the per cent of abnormally contracting segments can be computed from the difference between echographic and Fick stroke volumes[38]

All laboratories which routinely perform echocardiograms in patients with ischemic heart disease do not have the extensive experience quality of equipment and technical expertise of the groups who have published the results of their investigations in this area Thus the high degree of success in detecting segmental asynergy which has been reported in the literature may not be duplicated in some clinical laboratories

Nonetheless the echographic study of the left ventricle remains a useful adjunct in the evaluation of patients with ischemic heart disease The many potential applications of this noninvasive technique of assessing segmental wall motion are readily apparent The possibility of predicting the presence and anatomical location of ischemia even though echoes from the coronary arteries cannot be identified requires further investigation but remains exciting Perhaps the ultrasonic evaluation of the left ventricle during or immediately after exercise or pharmacological stress would provide such information Abnormal echocardiographic segmental wall motion prior to myocardial infarction could have important implications in patients with unstable or crescendo angina Another possible role for echocardiography would be monitoring the course and outcome of medical and surgical therapy for ischemic heart disease In fact changes in the echographic parameters of ventricular size function and wall motion after nitroglycerin administration and coronary artery revascularization have been reported[3, 6]

Echocardiography in acute myocardial infarction

In addition to its previously described use for the detection of segmental asynergy ultrasound has been utilized to monitor day to day changes in cardiac function to predict outcome and to diagnose complications in patients with acute infarction Each of these applications however must be considered unproven until further prospective clinical studies are reported

Serial echographic determinations of ventricular size and stroke volume index in patients with acute infarction have been found to correspond with clinical assessments of their studies[41] Nieminen and Heikkila[34] extensively evaluated left ventricular wall motion and function in patients with acute infarction They found abnormalities in all subjects but commonly used indices of over all left ventricular function did not correlate well with clinical status or eventual outcome However an index of the summed amplitudes of wall motion from seven different regions reflecting the degree of compensation of noninfarcted myocardium correlated closely with clinical parameters[34]

Corya and associates[31] serially studied a large group of infarction patients and found modest correlations between increased ventricular diastolic dimensions and clinical heart failure and between decreased PR–AC interval and the presence of a third heart sound More impressive however was the ability of a ratio of ventricular dimension to mitral valve closure time which was felt to be analagous to a volume/pressure index to predict eventual mortality of these patients DeMaria and co workers developed a similar echographic prognostic index which was very reliable in their hands These indices are based upon preliminary data and have not yet been demonstrated to be clinically useful If validated they may have a role in the assessment of therapeutic interventions when measured serially

Ultrasound has been used to study patients with several acute and chronic complications of myocardial infarction Right ventricular infarc

tion or interventricular septal rupture should be considered when disproportionate right ventricular enlargement is seen on the echocardiogram in the course of an acute infarction, especially in patients without pre existing pulmonary hypertension [43, 44] Day to day increases in mitral valve EF slope and CE opening amplitude were found to correspond with the appearance of a murmur of papillary muscle dysfunction by one group,[45] but these findings have not been confirmed by others [46]

A number of reports have described the echographic findings in patients with ventricular aneurysms [47-49] The most useful findings appear to be a sudden displacement of endocardial echoes as the ventricle is scanned, reduced or paradoxical wall motion, and disproportionately large left ventricular dimensions at the level of the apex Wall motion evaluation in uninvolved areas may be especially helpful in predicting the outcome of surgery in these patients [49] In addition, there has been one elegant report of a pseudoaneurysm of the left ventricle visualized echocardiographically [50]

Two dimensional echocardiography In recent years, several systems capable of two dimensional ultrasonic visualization of the heart have been developed These have overcome some of the shortcomings of single crystal unidimensional echocardiography in the evaluation of patients with coronary artery disease Much of the early work in this area was done by electrocardiographically synchronized stop motion B mode scanning utilizing a single element transducer [51] Several groups have calculated left ventricular volumes and ejection fractions from analysis of these B mode scans and demonstrated good correlations with ventriculographic data [5, 52] Teichholz and associates[53] studied 14 patients with coronary disease and asynergy by both traditional M mode echocardiography and B mode ultrasonography They were able to detect areas of asynergy in all 14 by the latter technique but in only seven of the 14 by the former In addition, the two dimensional methodology considerably improved the accuracy of their ejection fraction calculations

B mode scanning is both time consuming and technically demanding and it is therefore not well suited for clinical use Subsequently, a number of prototype instruments capable of real time display of two dimensional echocardiograms have been developed [53-58] Several production models are now commercially available and forthcoming improvements in instrumentation promise to further improve resolution and ease of operation Early experience with two dimensional real time echocardiographic systems suggested a wide range of potential clinical applications including the evaluation of patients with ischemic heart disease [59-61] Subsequent investigations have confirmed some of these expectations

Schiller and associates[6, 63] have gained extensive experience imaging the heart from the apex with an 80 degree sector scanner The views obtained with this transducer position, as well as from the precordium have significantly increased the portion of the ventricle which can be visualized and have allowed noninvasive biplane quantitation of left ventricular volumes and ejection fraction These investigators found good correlation between two dimensional echographic and biplane angiographic determinations of these parameters in 30 patients most of whom had coronary artery disease, suggesting that this technique may provide accurate data in this group of patients in whom M mode echocardiography is unreliable

Two groups have now published favorable reports evaluating the ability of two dimensional echocardiography to assess left ventricular wall motion Weyman and colleagues[64] were able to detect and localize ventricular aneurysms in 31 consecutive patients including 16 in whom M mode echocardiography failed to make the correct diagnosis Kisslo and associates[65] prospectively analyzed the correlation between two dimensional echographic and angiographic analyses of wall motion in 525 regions from 105 patients Only 18 per cent of these regions could not be visualized and 87 per cent of those imaged were correctly classified

Weyman and associates[66] recently reported their ability to visualize the left main coronary artery by cross sectional echocardiography They confirmed their identification of this structure by the intracoronary injection of cardiogreen dye while simultaneously recording the echocardiogram Clearly, more experience will have to be acquired before echocardiography can be used clinically to define such a critical aspect of coronary anatomy

If two dimensional echocardiography continues to live up to its early promise it would have

considerable advantage over both M mode echocardiography and other invasive and noninvasive techniques of wall motion analysis in patients with ischemic heart disease It allows patients to be studied repetitively without risk while in a basal state and it permits beat to beat analysis of contractions in real time As a result the effect of acute interventions such as exercise or changes in preload afterload or heart rate or the result of spontaneous events such as extrasystoles or the onset of angina can be analyzed Thus two dimensional echocardiography appears to be well suited for both the investigational and clinical study of patients with coronary artery disease

Most present two dimensional echocardiographic systems suffer from two major limitations which prevent the quantitative evaluation of the left ventricle in some patients The sector visualized from any single transducer position while significantly larger on more recent models is not always adequate to visualize the entire left ventricle In addition resolution of the endocardium remains a difficult technical problem Perhaps more important in limiting the availability and clinical use of this new technique is the *high cost of the* present equipment which approaches or exceeds $100 000 for some models

Summary

The initial general enthusiasm for echocardiography as a relatively simple and inexpensive noninvasive technique led to uncritical acceptance of some of its proposed applications Patients with ischemic heart disease have proven to be difficult to evaluate echographically by usual techniques because the *areas of the left* ventricle which are visualized *may not be* representative Thus, volume determinations and most indices *of contractile* performance while frequently providing helpful qualitative information have not been reliable in these *patients* Useful information about segmental wall motion abnormalities can be obtained from the echocardiogram when the involved areas *can be visual*ized but much of the ventricle is not routinely *examined* The role of ultrasound in patients with uncomplicated acute infarction remains predominantly investigational but ultrasound may be *helpful in the* evaluation of patients with complications of infarction or those who may concomitantly have other forms of cardiac disease

Although much work *continues* with M mode echocardiography the development of two dimensional real time ultrasonic equipment has added new impetus to the use of echocardiography in patients with coronary artery disease These instruments can visualize most if not all of the left ventricle and therefore are not subject to the inaccuracies inherent in evaluating M mode echocardiograms in patients affected by a segmental disease Several production models are currently available and many improvements in instrumentation can be anticipated Initial experience with two-dimensional echocardiography suggests that it is a valuable clinical and investigational tool but the relatively high cost of the present equipment may retard wide dissemination of this promising technique

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oxygen consumption and improves left ventricular contractility Ejection fraction increases after nitroglycerin when asynergic segments are present in viable but ischemic myocardium Blood flow redistribution from the epicardium to the endocardium has been shown with microspheres rubidium 86 and oxygen tension measurements at various myocardial layers

Valvular disease

In severe aortic regurgitation nitroglycerin infusion reduces afterload and improves hemodynamics by reducing regurgitant volume and improving left ventricular pump function Lower total stroke work reduced ventricular size and improved forward cardiac index delays left ventricular failure and progressive ventricular dysfunction

Reduction of systemic vascular resistance during nitroglycerin infusion in patients with mitral regurgitation augments forward ejection flow reduces regurgitant volume and relieves pulmonary vascular engorgement

Intraoperative hypertension

Prevention of intraoperative myocardial infarction is a primary anesthesia concern in the presence of coronary artery disease or with previous infarction Myocardial oxygen demand must be controlled Factors which increase myocardial oxygen demand include increased wall tension increased contractility or increased heart rate Kaplan and associates treating intraoperative hypertension with nitroglycerin showed significant reduction in mean arterial pressure central venous pressure and systemic vascular resistance without changes in heart rate cardiac or stroke index Improvements of ST segment depression occurred in 50 per cent of cases

Controlled hypotension

Nitroglycerin has been used to intentionally decrease blood pressure in order to minimize surgical blood loss Nitroglycerin has a short plasma half life no toxic metabolic products at pharmacologic doses and a low incidence of severe hypotension

History and physical characteristics

Nitroglycerin (glyceryl trinitrate $C_3H_5(ONO_2)_3$) was synthesized in 1846 by Sobrero Hering (1849) published the first paper on its effects in students and an 1853 monograph suggested the usefulness of this compound for treating angina pectoris cardiac edema epilepsy and headache On percussion nitroglycerin explodes violently and has been used as solid rocket fuel It is soluble in water to the extent of 1 25 mg /ml is extremely stable in neutral solution and has a low vapor pressure (0 00025 torr at 20° C) Saturated vapor in air is 0 33 p p m and can represent a commercial air pollution problem because it is readily absorbed through lipoidal surfaces of the skin and lungs

Metabolism and mechanisms of action

Nitroglycerin is rapidly metabolized in the liver by partial denitration catalyzed by gluthathione (GSH) organic nitrate reductase to 1 3 and 1 2 glyceryl denitrate (GDN) glyceryl mononitrate (GMN) and inorganic nitrate Most metabolites can be recovered in the urine within 24 hours Plasma half life of nitroglycerin appears to be 2 minutes in rats and man because of redistribution and rapid hepatic metabolism

Nitroglycerin reacts with vascular smooth muscle sulfhydryl groups leading to relaxation by the formation of disulfide linkage and release of inorganic nitrite Tolerance to chronic nitroglycerin exposure in man is associated with decreased tissue sulfhydryl concentration in vascular smooth muscle This can be quickly reversed by disulfide reducing agents such as dithiothreitol Tolerance develops because chronic nitroglycerin exposure produces disulfide linkage which cannot react further with organic nitrates Nitroglycerin tolerant individuals respond to other common vasodilator compounds (papavarine nitroprusside etc) suggesting that organic nitrates react at specific receptor sites distinct from other relaxant receptor sites

Preparation and administration

Despite its advantages intravenous nitroglycerin is not presently approved by the Food and Drug Administration for routine clinical use After obtaining an investigational new drug number (IND No) approval from Human Research Review Committees and informed consent nitroglycerin (0 015 per cent) may be obtained from Eli Lilly & Company Several methods for preparing therapeutic solutions of nitroglycerin have been described Nitroglycerin

Intravenous nitroglycerin

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Sublingual nitroglycerin has been administered for the relief of angina pectoris since 1853 Orally administered nitrates are rapidly metabolized and continuous intravenous nitroglycerin is presently used in carefully titrated amounts in critical care areas Indications for the use of nitroglycerin have been expanded to include reduction of infarct size in acute infarction, reduction of acute and chronic left ventricular decompensation by afterload reduction, reduction of pulmonary artery hypertension during coronary artery bypass, and induction of surgical hypotension The hypotension that results from venodilating properties of nitroglycerin may be physiologically better than hypotension from arterial dilators since cardiac output stroke volume, heart rate, and peripheral vascular resistance tend to remain stable while left ventricular end diastolic volume is reduced Incidentally since nitroglycerin does not produce arteriolar dilation, intracranial pressure increase is not seen in neurosurgical patients after nitroglycerin

Acute myocardial infarction

Experimental and clinical studies have shown that acute myocardial infarction is a dynamic process unfolding over many hours Reduction of oxygen consumption and/or work in the early phases of infarction may preserve ischemic myocardium and prevent necrosis Armstrong and colleagues have shown that nitroglycerin decreased left ventricular end diastolic and pulmonary capillary wedge pressure while maintaining cardiac index, heart rate and stroke volume in acute infarction with left ventricular failure Nitroglycerin dilates venous capacitance vessels more than arteriolar resistance vessels significantly reducing preload Coronary artery perfusion pressures are maintained after nitroglycerin

Nitroglycerin decreases coronary collateral flow resistance increases collateral flow and in dogs improves the endocardial/epicardial flow ratio in ischemic zones for up to four hours after nitroglycerin administration

Although precordial ST segment mapping has not yet been validated as a means of assessing myocardial ischemia in man, animal work suggests that ST segment changes measured by epicardial or precordial electrodes correlate with histologic evidence of ischemic damage as well as myocardial creatinine phosphokinase depletion Nitroglycerin reverses precordial ST segment changes and restores creatinine phosphokinase in acute myocardial infarction

Ventricular fibrillation threshold increases in animals and post infarction extrasystoles decrease in man after nitroglycerin

Tachycardia and systemic arterial hypotension with decreased coronary artery perfusion may occur during nitroglycerin infusion in uncomplicated myocardial infarction (pulmonary capillary wedge pressure < 12 torr) Controlled use of alpha adrenergic agonists may permit the use of nitroglycerin in this situation

Left ventricular failure

Nitroglycerin reduces afterload decreases left ventricular end diastolic pressure and myocardial

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Received for publication May 15 1978

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solution can be made by mixing crushed 0 6 mg tablets in sterile water to a concentration of 1 mg /ml filtering the solution through a milipor filter and storing in 30 ml vials This solution is stable for 21 days when refrigerated One vial (30 mg) is mixed in 250 ml of 5 per cent dextrose in water (120 μg/ml) Infusion should be started at 0 5 to 1 0 μg/Kg /minute to treat myocardial ischemia detected by electrocardiography, left ventricular decompensation (pulmonary capil lary wedge greater than 20 torr), or systemic blood pressure greater than 150 torr Induced hypotension requires larger doses to obtain signif icant decrease in mean arterial pressure

Monitoring

Hemodynamic measurements are extremely important when administering intravenous nitro glycerin Other than a precordial electrocardio gram, a balloon tip flotation catheter should be placed to measure cardiac output left ventricular end diastolic pressure and systemic pulmonary capillary wedge pressure Indices of myocardial function including right and left ventricular stroke work cardiac index, and pulmonary vascu lar resistance will be derived

Hazards

Decrease in coronary artery perfusion pressure leading to greater myocardial ischemia is possible if significant arterial pressure fall occurs Tachy cardia can occur in patients who have no evidence of left ventricular failure increasing myocardial oxygen demand Intramyocardial steal syn dromes have been reported but further investiga tion is needed for substantiation

A metabolic hazard may also exist For each mole of nitroglycerin metabolized one mole of nitrite (NO_2) is formed Hemoglobin oxidation to methemoglobin may occur in significant quanti ties especially in the presence of methemoglobin reductase deficiencies or in congenital M hemo globin variants

Drug interactions

Nitroglycerin prolongs pentobarbital sleep time because of microsomal oxidase inhibition and it may be an inhibitor of narcotic biotransforma tion Nitroglycerin potentiates the hypotensive and anticholinergic effects of tricyclic antidepres sants Synergism with other hypotensive agents has been reported

Summary and conclusions

Experimental and clinical evidence indicate that nitroglycerin can improve performance of an ischemic myocardium Simultaneously, regional myocardial oxygen supply may be increased by the vasodilating effects of nitroprusside on the coronary collateral vessels supplying the ischemic area Oxygen demand is decreased by reduction in left ventricular wall tension from afterload reduc tion Oxygen supply is increased in the ischemic myocardium, possibly reducing the severity of ischemia and actual infarct size

These effects strongly suggest that intravenou nitroglycerin is a valuable tool for the patien with myocardial infarction left ventricular fai ure, intraoperative hemodynamic changes (hy pertension), valvular disease, systemic an pulmonary hypertension, and for induced surgic hypotension (especially neurosurgery)

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Effect of transducer placement on echocardiographic mitral valve motion

Mitral valve prolapse is a common condition which often is readily diagnosed by clinical examination disclosing the typical non-ejection click and/or mid to late systolic murmur However such patients may present with unusual or labile auscultatory findings and left ventricular angiography has been required to establish the diagnosis in some cases The discovery that mitral valve prolapse can be accurately diagnosed in many patients using M mode echocardiography has been a great impetus to the study of this syndrome In patients with angiographically proven mitral valve prolapse various echocardiographi patterns have been described and are used to establish the diagnosis in patients with or without typical auscultatory features of the prolapse syndrome

In a group of 100 presumably healthy subjects, we performed echocardiograms to study the waveform of the mitral valve relative to other signs of prolapse and to tabulate the systolic mitral waveform specifically In the design of this study we attempted to assess the effect of transducer position on the mitral waveform by trying to record the anterior and posterior mitral leaflets and left atrium (or atrioventricular junction) with the ultrasound transducer located at the second, third, fourth and fifth intercostal spaces

During systole a single echo usually could be identified as continuously recorded from the point of leaflet apposition (C point) to the point of leaflet separation at end systole (D point) This echo was interpreted as representing the mitral valve leaflets in the area of coaptation and was analyzed for absolute anterior or posterior systolic motion A straight line was drawn from the C point to the D point (C D line) and deviation of the common continuous mitral e ho from this line was noted.

We found the echocardiographic patterns previously associated with mitral valve prolapse i e a hammock like smooth posterior motion beginning early in systole or a late systolic posterior motion could be obtained from some intercostal space in over 50 per cent of the subjects. We noticed that such patterns were more frequent when the transducer was located in the higher intercostal spaces, but less common in the same patients with the transducer located in the lower intercostal spaces Further analysis showed the angulation of the transducer on the chest wall was a major d terminant of the mitral val e ystolic pattern while the absolute intercostal space in which the transducer was placed was less important Extensive statistical work demonstrated an excellent correlation between the phonocardiographic findings and the echocardiographic patterns when the ultrasound transducer was in a position perpendicular to the chest wall when recording the mitral leaflets and left atrium Thus was considered the "perpendicular" position Regardless of the intercostal space if the transducer was pointed caudally patterns suggesting mitral valve prolapse were observed in many subjects without phonocardiographic evidence for this syndrome Conversely many patients with phonocardiographic evidence of prolapse did not have the echocardiographic features associated with this condition if the e hocardiogram was recorded with the transducer located low on the chest wall and pointing markedly cephalad In the latter situation the echocardiographic patterns associated with mitral valve prolapse usually were seen when repeating the study with the transducer located one intercostal pace higher and being perpendicular to the chest wall.

The sequence of recorded echocardiographic patterns with various transducer angulations was consistent with previous studies describing the motion of the base of the heart during the cardiac cycle During systole the base of the heart moves towards the apex as the annulus fibrosus moves caudally and anteriorly During systole the normal mitral leaflets close and passively follow the motion of the mitral annulus With the transducer located high on the chest the mitral annulus and leaflets move away from the transducer during systole as they descend toward the cardiac apex In this situation the D point will be posterior to the C point and a hammock shaped posterior motion may be recorded without regard to the presence of actual mitral valve prolapse Conversely when the transducer is located low on the chest pointing cephalad the mitral annulus and closed leaflets will move directly toward the transducer In this situation the D point will be markedly anterior to the C point The path of valve and annulus creates the smooth curvilinear anteriorly convex C D segment commonly recorded from such a low intercostal space With such transducer position and angulation, bulging of mitral valve leaflets as they prolapse toward the left atrium may not be apparent

This study has shown the importance of transducer angulation and position in standardizing the echocardiogram for assessment of the mitral valve systolic waveform using M mode echocardiography Recording both mitral leaflets and left atrium with the transducer perpendicular to the chest

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Coronary artery spasm—diagnostic and therapeutic implications

The hypothesis of coronary vasospasm as a cause of angina suggested by accurate clinical observations long ago began to be reconsidered recently on the basis of some isolated occasional angiographic observations made more by chance than by design during attacks of variant angina

The role of coronary vasospasm in angina pectoris at rest was confirmed in our institution by three series of studies

1 Continuous hemodynamic monitoring demonstrated that anginal attacks at rest characterized by S T segment elevation or depression were never preceded by an increase of the hemodynamic variables that control myocardial oxygen consumption Indeed the hemodynamic pattern observed consistently during these attacks was remarkably similar to that observed during experimental transient coronary occlusion

2 Regional myocardial perfusion studies by Thallium 201 scintigraphy during anginal attacks showed massive transmural deficit of perfusion in patients with S T segment elevation and in more recent studies severe diffuse or subendocardial flow reduction in patients with S T segment depression

3 Coronary angiography during attacks demonstrated a severe spasm of one or two major coronary vessels in patients with S T segment elevation and a spasm of a small branch or presence of collaterals or diffuse lumen reduction of several branches in patients with S T segment depression

The degree of atherosclerotic involvement of the patients with vasospastic angina was extremely variable from normal coronary angiograms to severe triple vessel disease The spasm appears to involve the vessel over a long segment and in the presence of organic stenosis extends proximally and/or distally to the lesion Our studies indicate that the electrocardiogram may show S T segment elevation or depression depending on the predominantly transmural or subendocardial distribution of myocardial ischemia Both patterns may be sometimes observed in the same patient during angina at rest depending on the severity of the vasospasm

The objective demonstration of the possible role of coronary vasomotoricity reducing myocardial perfusion suggests a revision of the traditional notion that angina ensues only when myocardial metabolic demand increases beyond the possibility of coronary reserve (set by the degree of coronary stenosis and of collateral development) Indeed the concept that the *only* variable capable of determining an acute imbalance between demand and supply is an excessive increase of myocardial demand has so far conditioned medical and surgical approach to angina Yet the demonstration that angina at rest is not preceded by a rise of the determinants of oxygen consumption indicates that it is not secondary to this mechanism

In our experience the borders between primary vasospastic angina and traditional secondary angina are very ill *defined* because on the one hand some patients with variant angina (usually a reasonable landmark of vasospastic angina as suggested by Prinzmetal) may also have effort induced angina with fixed reduced exercise tolerance on the other some others may develop occasionally vasospastic angina on exertion Finally alpha tone appears under some circumstances capable of reducing coronary reserve and a severe reduction of myocardial perfusion was demonstrated in patients during angina induced by pacing

The diagnostic evaluation of patients with angina at rest should aim to demonstrate whether or not onset of S-T segment changes (not of chest pain which is always a late phenomenon) is preceded by increased metabolic demand beyond the possibilities of supply In most cases the determination of the double or triple product at the onset of the attack and at the onset of ischemia during a graduated effort or a pacing test may serve the purpose

The therapeutic approach of these patients is substantially different from that of the patients with angina secondary to excessive increase of demands for whom beta blockers and coronary surgery represent a rational approach Since cardiac denervation does not prevent coronary vasospasm medical treatment with high doses of nitrates and calcium antagonists such as verapamil represents in our experience so far the most effective form of treatment for patients with vasospastic angina

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wall or pointing very slightly cephalad is the optimal way to obtain records for analysis of possible mitral valve prolapse by echocardiography

Published echocardiograms should include a description of the location and angulation of the transducer on the chest wall especially when dealing with the mitral valve pattern associated with anatomic prolapse

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Hazards of cardiac catheterization in children with primary pulmonary vascular obstruction

Primary pulmonary vascular obstruction (PPVO) in children is rare and affects both sexes equally It is generally rapidly progressive and is usually fatal often suddenly with a few years of onset of symptoms The cause is unknown and no effective form of therapy is available PPVO can usually be diagnosed non invasively and obstructive lesions resulting in pulmonary artery hypertension such as mitral valve stenosis supravalvar mitral ring cor triatriatum and pulmonary venous occlusive disease can usually be excluded by physical examination electrocardiography chest x ray and echocardiography However cardiac catheterization often hazardous in these very hemodynamically unstable patients[1] is still undertaken to confirm the diagnosis of PPVO and assess response to medical forms of therapy such as oxygen tolazoline and isoproterenol

The following data represent our experiences with cardiac catheterization and the complications encountered in these patients during the past 25 years Thirty two catheterizations were performed in 24 patients 13 females and 11 males ranging in age from 1 month to 19 years (median 11 years and 4 months) Pulmonary artery (PA) saturation ranged from 20 to 77 per cent (median 65 per cent less than 60 per cent in over one third) systemic artery (SA) saturation 75 to 98 per cent (median 94 per cent) pulmonary blood flow 0 7 to 5 2 L/min/M^2 (median 2 9) and PA systolic pressure was equal to or greater than the SA value in 80 per cent There was no significant difference in these parameters between children who did and did not develop complications during the procedures Among three patients recatheterized at a median interval of five years following the initial procedure the PA systolic pressure had increased by 31 to 122 per cent Oxygen administered to 11 patients resulted in a PA systolic pressure reduction (by 25 per cent) in only one and tolazoline PA infusion in the same number resulted in a PA pressure increase in five without significant change in the other six Isoproterenol PA infusion utilized in only one patient did not decrease PA pressure The incidence of complications did not appear related to these maneuvers

Major complications occurred in six patients and minor episodes in a similar number (Table I) The major complications consisted of episodes of sinus bradycardia with hypotension of sudden onset with the venous catheter in the pulmonary artery in three patients (Nos 1 2 and 3) with a fatal outcome in one child (No 2 1977) In this latter patient the episode commenced during percutaneous placement of an arterial line Another patient died (No 4 1953) immediately following completion of the procedure with sudden onset of nausea and gasping respirations initially without electrocardiographic change followed in minutes by ventricular fibrillation The PA saturation had decreased from 47 to 20 per cent toward the end of the study A third fatality (No 5 1960) occurred immediately after general anesthesia administered before direct left atrial puncture attempted to exclude left atrial outflow obstruction The sixth major episode consisted of transient ventricular fibrillation after simultaneous injection of contrast material into the main pulmonary artery and left atrium (1966) normal sinus rhythm being restored by cardioversion The six transient minor complications consisted of nausea and vomiting (four) agitation with anoxia (one) and with chills (one)

In addition two patients died suddenly on the day after catheterization and yet another four within three weeks

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Table I Catheterization data of 12 patients in whom complications occurred

Patient No	Age (yrs)	O saturations		Pressures (mm Hg)			Complications
		PA	SA	RA a"	PA	SA	
1	3 5/12	49	90	9	154/91	9?/57	Transient sinus bradycardia and hypotension with catheter in PA died suddenly three days later
?	10 11/12	47	?	1?	118/65	?	Sinus bradycardia with catheter in PA then ventricular fibrillation and death
3	13 8/12	63	94	1?	150/110	110/70	Transient sinus bradycardia and hypotension with catheter in PA
4	19	?0	75	?	130/100	88/65	Decrease in PA sat 47→?0% then nausea gasping ventricular fibrillation and death
5	10 11/1?	54	93	13	120/?0	110/?0	Died immediately following general anesthesia
6	3 7/1?	57	90	12	105/55	100/80	Following simultaneous MPA and LA angiography developed ventricular fibrillation which was cardioverted
7	8/1?	50	88	9	112/52	8?/4?	Transient nausea and vomiting died suddenly next day
8	12 11/1?	59	95	12	109/72	?9/50	Transient nausea and vomiting
9	13 10/12	77	96	6	150/80	116/66	Transient nausea and vomiting
10	14 9/12	66	91	14	118/67	118/87	Transient nausea and vomiting
11	11 9/12	56	97	15	111/71	108/72	Transient agitation and anoxia
12	17 ?/12	75	95	9	135/45	135/67	Transient agitation and chills

Abbreviations PA = pulmonary artery SA = systemic artery RA = right atrium LA = left atrium

following the study emphasizing the extremely brittle status of these patients

Fatalities associated with cardiac catheterization among patients mostly adults with PPVO have previously been reported At least four deaths occurred during the study and at least a similar number died immediately following completion of the procedure While a variety of arrhythmias have been recorded among all deaths it is noteworthy that a very slow ventricular rate due either to sinus bradycardia or atrioventricular block has occurred frequently Histologically abnormalities of the arterial vessels supplying both the sinoatrial and atrioventricular nodes in patients with PPVO have been described While direct trauma by the catheter to these areas does not seem to have induced the bradycardia in most as the catheter was usually in the PA at the time it is conceivable that any further reduction of an already reduced pulmonary blood flow could lead to further node impairment Angiography in the main PA was followed by death in one patient and by ventricular fibrillation successfully cardioverted in one of our own Should angiography be deemed necessary in a patient whose mean PA pressure exceeds 40 mm Hg selective right and left pulmonary arteriography are considered less hazardous Among our patients we observed no significant PA pressure reduction in response to either oxygen tolazoline or isoproterenol, in contrast to other investigators.

In view of our own experience as well as a review of the English language literature we may state that cardiac catheterization in patients with PPVO is an unusually hazardous, often fatal, undertaking One sympathizes fully with attempts to exclude by means of definitive physiologic studies and angiography the presence of remediable left sided obstructive lesions in clinical situations suggesting PPVO Still one has to balance the urge to leave no stone unturned against the high risk of the procedure Possibly the recently introduced sophisticated techniques particularly echocardiography may shift prudent cardiologists toward the non invasive route in these desperate situations

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wall or pointing very slightly cephalad is the optimal way to obtain records for analysis of possible mitral valve prolapse by echocardiography

Published echocardiograms should include a description of the location and angulation of the transducer on the chest wall especially when dealing with the mitral valve pattern associated with anatomic prolapse

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Hazards of cardiac catheterization in children with primary pulmonary vascular obstruction

Primary pulmonary vascular obstruction (PPVO) in children is rare and affects both sexes equally It is generally rapidly progressive and is usually fatal often suddenly with a few years of onset of symptoms The cause is unknown and no effective form of therapy is available PPVO can usually be diagnosed non invasively and obstructive lesions resulting in pulmonary artery hypertension such as mitral valve stenosis supravalvar mitral ring cor triatriatum and pulmonary venous occlusive disease can usually be excluded by physical examination electrocardiography chest x ray and echocardiography However, cardiac catheterization often hazardous in these very hemodynamically unstable patients is still undertaken to confirm the diagnosis of PPVO and assess response to medical forms of therapy such as oxygen tolazoline and isoproterenol

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Of atherosclerosis in infants and children and viral infections

That atherosclerosis is common in infants and children is well known What is not known is why Why should infants and children have atherosclerosis if the risk factors for atherosclerosis are hypercholesterolemia hyperlipidemia hypertension smoking caffeine intake tension and anxiety states wear and tear the aging process etc? These factors would not have existed very long if they existed at all in infants and young children Perhaps these factors are not the etiologic agents at all but are only aggravating or contributing factors which require many years of existence and therefore can manifest their influence only in adults if the individuals live long enough Surely the calcific lesions of arteriosclerosis of adults are not found in infants and young children Calcification of arterial plaque requires a long time just as calcification of lesions in other tissues of the body requires a long time

But viral infections do occur regularly in infants and children and infections produced by viruses are well known to be highly infectious and even highly lethal in infants and children Furthermore the picornaviruses such as the Coxsackie B group of viruses which commonly infect the upper respiratory tract of infants and children can severely damage the blood vessels of suckling mammals including man These arterial lesions could be the initial lesions of the atherosclerotic plaques found in very early life of man The atherosclerotic plaques would be the healed" or healing lesions of the locally infected arteries and infected and damaged vasa vasorum These plaques are of course found in the arteries and not in the veins even though the risk factors and the viral infections apply to the veins as much as they do to the arteries But the intravascular pressure is much higher in arteries than in veins and arteries and veins are certainly morphologically different Thus the healing or reparative processes of sites of viral infection and damage in the arteries of man especially of infants and children could result in atherosclerosis Therefore smoking caffeine intake hypertension hypercholesterolemia hyperlipidemia and the other commonly listed risk factors would really not be necessary for atherosclerotic plaques to develop but would only cause the plaques to develop more rapidly more extensively and more frequently and seriously and to differ morphologically biochemically and functionally The only initiating risk factor then would be the viral infection by the proper viruses whether they be known or unknown

These concepts not only have merit as thoughts but also have factual support The role of viruses in the production of atherosclerosis and arteriosclerosis needs thorough investigation as limited studies already indicate Furthermore if certain viruses are prone to initiate arteriosclerosis then the potential for prevention of arteriosclerosis by vaccines is considerable The possible role of even bacterial infection (tuberculosis pneumococcus staphylococcus typhoid etc) as the initiating cause of arteriosclerosis was suggested at the beginning of this century The role of viruses in infectious diseases was poorly known then and not even considered by the early investigators Viral infection as an important disease of blood vessels needs serious and extensive investigation and research support

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report I repeat my concluding sentence that only a *formal* prospective epidemiological study can be expected to provide valid conclusions " Incidentally the New York marathon 1977 attracted 4 823 official starters of whom 3,701 finished. 3 876 officially finished the Boston marathon 1978 That I am an experienced marathoner (as is Bassler[1]) is quite irrelevant to the issue at hand

As far as the medical justification for moderate exercise among post infarct men (as well as marathoning for those able to achieve this le el of activity) I would agree with Bassler Terry Kavanagh and others have clearly documented the validity of this approach although only about 2 to 3 per cent of Kavanagh s rehab patients can achieve the full marathon goal

The unfounded hyperbole in which Bassler engages when he endlessly repeats his anecdotal stories about absolute CHD immunity among 42 km men is scientifically unjustified and misleading It is potentially dangerous to the medically unsophisticated average runner

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Acid gas induced MI

To the Editor

In the textbooks of cardiology we were not be able to find any report of acute coronary events following exposures to gases or vapors In one of our patients, the symptoms of acute myocardial infarction appeared immediately after the inhalation of a mixture of ammoniacal and acetic acid gases The patient a man of 46 a mild smoker (15 cigarettes a day) with neither previous symptoms of coronary heart disease nor disorders of lipidic or glycidic metabolism experienced substernal pain when he inhaled gases produced by a photographic developing set (sodium hydroxide sodium sulphite ethylendiamine plus ammonium tyocianate acetic acid and HPN a zirconium salt) The pain recurred twice in the night and in the following day he was admitted to our coronary care unit, where an inferior wall infarction was diagnosed (electrocardiographic and enzymatic confirmation)

After recovery from acute myocardial infarction effort angina persisted for some months indicating in our opinion anatomic coronary damage (no angiography could be performed) however the strict relationship between gas inhalation and onset of symptoms suggests a possible triggering effect of the former

We would greatly appreciate your opinion and the views of any of your readers about this possibility

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Pathogenesis of myocardial infarction

To the Editor

The recent correspondence by Drs Penther and Baroldi highlights yet again the controversy about the pathogenesis of myocardial infarction Because our published work is discussed by both correspondents we are grateful to the Editor for allowing us to comment further We submit that the problem is one of definitions We agree with Dr Baroldi that one must not confuse the different types of myocardial necroses frequently associated with this disease " which is the nub of the whole controversy If the view is taken that all myocardial necroses from large macroscopic areas to microscopic foci, are to be regarded as myocardial infarction then it is scarcely surprising that there is wide divergence in the reported results of surveys of the relation of coronary thrombosis to myocardial infarction

In our survey we chose a somewhat arbitrary macroscopic definition of a regional transmural infarct deliberately to exclude other forms of ischemic myocardial necrosis encountered in coronary heart disease The myocardial necrosis was confirmed in all our cases by microscopy and no case had been subjected to cardiac surgery Regional myocardial infarction as we defined it is common in patients dying of ischemic (coronary) heart disease and in the majority of cases is associated with a classical history of chest pain and the area of necrosis can be localized by ECG as anterior inferior or lateral We find the incidence of occlusive coronary thrombosis in such cases to be over 90 per cent We are well aware that regional infarction is not the only form of myocardial necrosis seen in ischemic heart disease In patients with longstanding coronary heart disease associated with multiple zones of coronary artery stenosis often of the triple vessel pattern multiple foci of myocardial necrosis varying from about 1 cm in diameter to microscopic lesions may be detected The subendocardial region and the centers of the papillary muscles are particularly affected and in extreme cases the whole subendocardial zone may be necrotic in which case the term diffuse subendocardial, or laminar infarction would seem appropriate The extreme degree is uncommon but lesser degrees of focal necrosis are frequent and identification of the latter may be possible only on microscopy of several blocks of myocardium. Such cases were excluded from our study

The pathophysiology of diffuse subendocardial necrosis has been beautifully elucidated by Hoffman and Buckberg as a failure of intramyocardial perfusion from a variety of conditions, some of which do not involve any abnormality of the

Letters to the Editor

Statistics marathoning and CHD

To the Editor

Milvy suggests that the absence of fatal CHD among marathon runners is not statistically significant (AM HEART J 95 538 539 1978) He argues that a cohort of 9 958 male marathoners would generate only one or two CHD deaths per year because they are all lean young nonsmokers This number of deaths is too small to measure any protection marathoning might offer However the *number of marathon ers at risk* is closer to one million than to the 9 958 suggested by Milvy

Our report edited by Milvy clearly states that all mara thoners past and present are under our world wide surveil lance Cases from four continents covering five decades are included The marathon distance has been popular since the turn of the century Race results and autopsy slides are permanent Since marathons have been timed in excess of eight hours anyone who even walks the distance is covered A million runners could generate one CHD death *per day* if the life style offered no protection at all[1]

And all runners are certainly not lean young nonsmok ers I have personally covered the 42 km distance with more than a hundred graduates from Cardiac Rehabilitation Programs including 33 with myocardial infarction 16 with bypass grafts and others with double vessel and triple vessel *disease This cohort of cardiac marathoners could generate* one or two CHD deaths per year if the life style offered no protection at all[1]

Milvy is an experienced marathoner He has participated in the New York and Boston races popular courses which attract nearly 10 000 runners each year Larger races have been seen in Europe Africa and Asia With 10 000 runners participating in a single race I doubt that Milvy believes there are only 9 958 male marathoners I can only conclude that his statements in the journal were delayed by several years and are now out of date

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Reply

To the Editor

Between 1972 and 1976 Bassler sent at least 27 letters to medical and scientific journals asserting that marathon running absolutely protects the marathoner from death from ischemic heart disease or alternatively from atherosclerosis or coronary heart disease More of his letters have recently appeared indicating that it is the marathoner s life style that confers this remarkable immunity to CHD In 1972 he said in an early prototype *of these letters[2] that a search of* the literature failed to document a single death due to coronary arteriosclerosis among marathon finishers The only extensive paper by Bassler that seeks to document these unsupported claims has appeared rather ex post facto in the New York Academy of Sciences Marathon Conference Annals[3] to which Bassler makes reference in his most current letter In his Methods section of this paper he writes that An excess of 200 reports (of deaths among marathoners) have been received during the past 10 years Many are duplicates *Most were below the 42 km threshold Brown and Milvy in* a critique of this paper comment that it would have been more impressive had the total case load relevant to the hypothesis been provided (22 cases including the legendary Pheidippides are reviewed in the paper Their ages a critical factor in determining risk of CHD are mentioned in only nine of these 22 cases)

In his most recent letter commenting upon my annotation Bassler informs us that he knows of no deaths from CHD among one million marathoners past and present yet fails to inform us of the validity of his data base How many of these one million men and women have died? How many death certificates did he examine? Bassler insists that CHD not only be clinically proven but confirmed by autopsy and histo logically proven How many autopsy reports did he obtain? How many sets of histological slides did he review? We look in vain for such essential data!

In his Methods section[3] he further indicates that deaths in marathoners are reviewed worldwide Since great differences in the incidence of CHD exist in the underdeveloped devel oping and industrialized countries it would be helpful f Bassler sometime somewhere to provide a careful breakdown of where this marathon cohort of one million comes from and how he can keep abreast of deaths from such a large disparate group Bassler correctly asserts that if his hypothesis is sound these one million marathoners will generate about ½ to 1 CHD deaths per day (if they average about 30 years of ag the age of the average U S marathoner) In the age group 25 to 34 years in which 8 per cent of U S deaths are from major cardiovascular diseases the death rate from all causes is 2 145 per million per year For the world at large the WHO estimates it to be only slightly higher Ninety per cent of all scientists who ever lived are alive today I do not know if an equal per cent of these million marathoners are currently alive but unless Bassler is inspecting about 2 000 perma nent sets of pathology slides of dead marathoners per year his world wide surveillance is not thorough That s 20 000 sets of marathoners slides per decade that should be available for his study! Yet in spite of his worldwide surveillance he comes up with only 200 cases mostly duplicates mostly less than full marathon distance and reports upon only 22 cases in any scientific and non anecdotal way Where have the other *199 8* dead marathoners gone? Or perhaps there aren t a million marathoners in the first place!

Finally I used 1975 figures for my analysis The latest reasonably accurate figures we have available as of March *1978 are that about 23 000 U S men completed* a marathon in 1977 By multiplying my data by 2½ we may update my

report I repeat my concluding sentence that only a *formal* prospective epidemiological study can be expected to provide valid conclusions " Incidentally the New York marathon 1977 attracted" 4 8?3 official starters of whom 3 ?01 finished. 3 876 officially finished the Boston marathon 1978 That I am an experienced marathoner (as is Bassler?) is quite irrelevant to the issue at hand

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Pathogenesis of myocardial infarction

To the Editor

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The pathophysiology of diffuse subendocardial necrosis has been beautifully elucidated by Hoffman and Buckberg as a failure of intramyocardial perfusion from a variety of conditions some of which do not involve any abnormality of the

major epicardial coronary arteries This type of lesion may be seen for example following cardiac bypass operation where coronary artery perfusion has been inadequate Severe stenosing coronary atherosclerosis may have the same effect and no recent occlusion is required to precipitate muscle necrosis although it can obviously do so

We are currently conducting a prospective study of ischemic myocardial necrosis in which the necrosis is assessed and categorized by histochemical techniques and the coronary arteries dissected from the hearts are examined independently by histological techniques Our preliminary findings indicate that single regional infarcts in cases without previous myocardial damage are always associated with recent thrombotic occlusion of the supplying coronary artery whereas in cases of advanced coronary atherosclerosis with triple vessel disease and myocardial scarring focal and subendocardial necroses are common findings but the incidence of recent coronary thrombosis is lower We believe that this study will emphasize the important role played by case selection in determining the incidence of recent coronary thrombosis related to the various forms of myocardial necrosis

The question as to which form of myocardial necrosis is the most important in terms of morbidity and mortality is another matter Certainly the circumscribed regional infarct is the most easily recognized by pathologists perhaps giving a spurious view of its frequency In current hospital practice with intensive and coronary care units widely available more cases of long term severe coronary atherosclerosis are dealt with Necropsies from this group provide a higher proportion of examples of complex myocardial damage

The question of whether coronary thrombosis causes or is secondary to myocardial infarction is probably best answered by in vivo studies using radioactive fibrinogen It seems to us that the meticulous studies of Fulton and Sumner showing that coronary thrombi have a radionegative head provide the best evidence that coronary thrombosis antedates myocardial damage If the opposite view is taken then an explanation is required for the finding of recent coronary thrombosis in a not inconsiderable proportion of cases of sudden cardiac death due to coronary atherosclerosis without evidence of myocardial necrosis

Finally we would make a plea for a more precise and agreed set of definitions for the various forms of ischemic myocardial necrosis so that those interested in the subject can compare like with like Pathologists owe it to their clinical colleagues to sort out the confusion that currently prevails a situation that can only bring morphologic studies and morphologists into disrepute

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Reply

To the Editor

Dr Davies and associates explain the wide divergence of the frequency of the occlusive thrombus by the lack of distinction between subendocardial or laminar infarctions (from 1 cm. in diameter to microfoci detectable only histopathologically) in general without a thrombus and regional infarcts most of which are associated with an occlusive thrombus About the same opinion is shared by other authors

In classifying the different diseases an entity is generally profiled according to the pathognomonic clinical and pathologic parameters independently from the size of a lesion. In order to investigate the natural history of the acute myocardial infarction in our study only patients who died in hospital because of a classical acute pattern of this disease (chest pain ECG typical changes etc) without any other disorder and with postmortem documented myocardial *coagulation necrosis* were selected The distribution of both the size of the pathognomonic necrosis (in per cent of the left ventricular mass) and the frequency of an occlusive thrombus was as follows

Table I

Size (%)	*Total cases*	*Cases + thrombus*
< 10	29	4
11 20	20	7
21 30	25	10
31 40	11	5
41 50	12	9
> 50	3	3

In the group of 29 cases with a size inferior to 10 per cent only 12 cases were subendocardial i e the coagulation necrosis was not seen with the naked eye and detected histologically In the other 88 cases this type of necrosis was unifocal very often transmural and with a diameter much greater than 1 cm Following the distinction of Dr Davies I don t think that they can be called subendocardial or laminar On the other hand if they are regional the over all frequency of the thrombus is 43 per cent However if we compare the 73 cases with a size minor or equal to 40 per cent and the 15 cases with a size superior to 40 per cent the thrombus frequency is 35 6 and 73 3 respectively This difference is statistically significant (χ = 7 26) and suggests that there is a trend of an increasing frequency of the thrombus in relation to the increasing size of the coagulation necrosis Since Dr Davies mentions some preliminary results in cases

without previous myocardial damage it is important to note that we were unable to see any relationship between thrombus frequency and the size of a scar (present in 6 of our cases 44 of which had a subendocardial scar) A first consideration seems appropriate namely that the distinction between small and large or regional infarcts is cloudy and perhaps it is better to size the extension of the coagulation necrosis as a per cent of the total left ventricular mass I suspect that a selection of the material on the basis of the major diameter only may include mainly very large infarcts If this is the case we agree on the very high frequency of the thrombus

However I have to repeat that the core of the controversy is not the frequency of the thrombus but its significance in further reducing the flow (see my reply to Dr Penther s letter[3]) since it is generally located in a severe old stenosis preexisting for a long time prior to the onset of the infarct It sounds logical to presume that this long lasting silent period can be interpreted only by the presence of functioning collat erals Therefore the thrombus occurs in an already bypassed stenosis

I am very sensible to the plea of Dr Davies for a better understanding of the so called ischemic lesions One may agree or disagree on my definition of the different types of myocardial necrosis but nevertheless it is an attempt along this line Keeping in mind that when I speak of different types of necrosis I mean their different nature—and likely with a different pathogenesis—as suggested by the clear cut distinc tion in terms of the structural changes So for instance the type of necrosis seen after cardiac bypass surgery—we are tudying that—looks more like myocytoly is than coagulation necrosis and several facts support the view that myocytolysis may be a primary metabolic lesion and not an ischemic one Obviously the field becomes confused when we try to under stand more but this confusion is welcome if we will be able to improve our knowledge Disrepute will result only if we are investigating a problem without considering all the variants or if we speak of necroses without a distinction of their nature

Finally a last comment on the best evidence that coronary thrombosis antedates myocardial damage given by the demonstration that coronary thrombi have a radionegative head

Unfortunately the injection of radioactive fibrinogen is carried out hours after the appearance of the first clinical symptoms Therefore the radio negativity does not exclude that a thrombus is secondary It shows only that the throm bus was formed before injection not if it is primary or secondary On this subject in 106 witnessed cases of unex pected sudden coronary death 7? died within 10 minutes 29 in one hour and five in 5 hours The frequency of an occlusive thrombus was 13 9 and zero respectively This shows that a thrombus when present is a very early phenomenon

Finally the last question of Dr Davies i e how to explain a recent thrombus without evidence of myocardial necrosis again in cases of sudden coronary death In my hypothesis on the secondary thrombus forma ion I always mentioned the possibility that an increased peripheral resistance may be the starting mechanism or at least one of the mechanisms as for in tance in large infarcts (impairment of the intramuscular flow) In the past few years more and more evidence is given that a coronary spasm is a fact and not an artefact—I don t know if primary or secondary to angina or infarction Howev er if it is a fact it may increase the peripheral resistance and may become the cause of a thrombus as recently suggested even in the absence of myocardial infarction

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Orthostatic hypertension in normotensives and borderline hypertensive patients

To the Editor

The study of Hull and associates by means of a non invasive procedure confirms the high percentage of orthostat ic diastolic hypertension previously observed in borderline hypertensive patients during 70-degree head up tilt However the distinction between normotensives and borderline hyper tensive patients remains difficult and there is still an overlap which concerns 30 per cent of this latter group

In our study of 85 borderline hypertensive patients we measured the hemodynamic changes during tilt and the results provided an explanation for the differences in the orthostatic behavior of the borderline group It was obvious that orthostatic diastolic hypertension closely corresponded to the borderline hypertensive patients with elevated cardiac output neurogenic mechanisms were considered to play a predominant role in this group In contrast the orthostatic responses of the borderline hypertensive subjects with normal cardiac output were similar to those observed in normoten sives It may be concluded that orthostatic diastolic hyperten sion is a useful but not decisive procedure in the assessment of the borderline status

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Chest thumping to terminate ventricular tachycardias

To the Editor

Chest or precordial thumping to terminate ventricular tachycardia can be fraught with risk and should be performed *only when equipment for external defibrillation is immediate*ly available Yakaitis and Redding indicated that thumping can lead to ventricular fibrillation and have recommended its deletion in the treatment of cardiac arrest Pennington and colleagues study also revealed an incidence of conversion of ventricular tachycardia to ventricular fibrillation following chest thumping

With the possibility *of provoking a more dangerous arrhyth*mia with a thump electrical cardioversion or drug therapy should be the treatment of choice

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3 *Pennington J E Taylor J and Lown B Chest* thumping for reverting ventricular tachycardia N Engl J Med 283 1192 1970

Reply

To the Editor

Our present experience with the use of chest thump and other mechanical means for the conversion of ventricular and *atrial arrhythmias extends to a group of close to 70 patients* The whole of our experience is now in press under the title of Mechanical stimulation of the heart Its therapeutic value in tachyarrhythmias to be published in the Journal *Chest* We have not encountered one single episode of precipitation of ventricular *fibrillation after the application of a chest thump* for the treatment of ventricular tachycardia It is important to know however that many patients if allowed to remain in ventricular tachycardia may degenerate into ventricular fibrillation No doubt these two arrhythmias are intimately related *and of course one should always be prepared to treat* ventricular tachyarrhythmias by electrical defibrillation

The article quoted by Dr Forester in his letter that of Yakaitis and Redding[2] refers mostly to an experience in an experimental animal It does not refer to the actual use in patients The article by *Pennington* Taylor and Lown in fact advocates the use of thumping as a means of converting ventricular tachycardia In the one instance they mention of the appearance of *ventricular fibrillation is not clear whether* it was precipitated by the thump or if it was the natural result of prolonged ventricular tachycardia

We feel that chest thump is not only a viable means of treatment but in fact advocate this modality as the first line *of attack in the* appearance of ventricular tachycardia particularly when the patient has physical evidence of ventricular aneurysm Of course we also feel that drug and electrical conversion should be available and may be necessary in some instances Furthermore we advocate the use of external, as well as internal stimulation via a catheter as a safe easy to perform first line of treatment in patients with ventricular *tachycardia as well as in patients with asystole in whom the* induction of an ectopic ventricular beat may start an organized rhythm

As we gain more experience with the use of mechanical stimulation of the heart we will be better equipped to deliver the mechanical stimulus to the area which is *either part of the* reentrant mechanism or is closest to the point of origin of the ectopic rhythm The application of mechanical stimulation is presently being pursued both in patients in the Coronary Care Unit and in patients in whom intracardiac catheters have been introduced for either diagnostic or therapeutic reasons

A better understanding of the pathway of reentrant arrhythmias will allow a *more* rational use of low energy mechanical stimulation in the treatment of these tachyarrhythmias This has been under intensive study in several centers in the last few years

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Observations on Q fever endocarditis

To the Editor

The report of a case of Q fever endocarditis by Dr Applefeld and colleagues (AM HEART J 93 669 1977) was welcome to those of us who have long wondered why this complication has been recorded so infrequently in the *United States* where in some areas at least both overt and subclinical Q fever infection in humans is far from rare It was of particular interest since indirectly it drew attention to the problem of diagnosis and the difficulties in management that might have ensued had the patient not *died so soon after the* date of the initial serological tests *for Coxiella burneti* (C burneti) As it is not clear from the case report I am assuming that the results of the initial tests were not available before the *death* of the patient

The diagnosis was far from proven. Although signs and symptoms of subacute infective endocarditis were present, the titer of phase I complement fixing antibody of 1:32 was well below the lowest level (1:200) which the WHO Scientific Group on Rickettsial Diseases in Man considered suggestive of Q fever endocarditis. All 3? symptomatic patients described in two recent reports had phase I antibody titers of 1:128 or above. Particularly unusual and difficult to explain in the Baltimore case was the very low initial titer of phase II complement fixing antibody when the titer for phase I antibody was already 1:32. In none of the patients studied by Powell and Stallman, where the phase II titer was negative or 1:8, was phase I antibody detected. Evidence of the fourfold rise in phase II antibody, itself an indication of acute infection or re-infection rather than chronic infection, was available only after death. Taken alone, elevated titers of phase I antibody usually indicate prolonged infection in the past, especially in a patient with a complication such as rheumatic mitral valvular disease, but do not necessarily indicate present persisting infection. Elevated phase I titers, some as high as 1:128, have been found in completely asymptomatic patients with and without valvular heart disease. However, since the antibody to phase I antigen is probably a neutralizing antibody, it is possible that during the period prior to the development of phase I antibody lack of neutralization allows seeding of the organism to occur. Patients with low or absent titers of phase I antibody may have chronic Q fever in evolution. A proven case with elevated titers of only phase II antibody[9] has already been cited by Dr. Applefeld and colleagues; in that patient the organism was eventually isolated at autopsy four months later, not from the valve but from the spleen. In another case where the titer of phase I antibody was only 1:64, the organism was isolated not only from the blood during life but also from aortic and mitral valves postmortem. Previous treatment with tetracycline may also explain lower titers in some patients.

With this evidence and knowing what an indolent and destructive disease Q fever endocarditis can become, the physician faced with a patient with infective endocarditis and only slightly elevated titers of phase I antibody cannot afford not to initiate appropriate antibiotic therapy immediately, even if, as in the Baltimore patient, the titer of phase II antibody is very low too. It would also be wise to start such treatment in those patients where the combination of valvular heart disease and only slightly elevated titers of phase I antibody occurs in the *absence* of signs of infective endocarditis, as the fatal case reported by McIver demonstrated that it may take months after the attack of acute Q fever for those signs to develop. Traditionally tetracycline is considered to be the drug of choice, but lincomycin used in combination with tetracycline may be even more effective in controlling the disease. The patient in whom this regime was originally employed received these antibiotics alone for just over five years. Four years and nine months after stopping antibiotic therapy she is alive and in good health, the longest survivor so far reported.

Finally, it is not correct to state that clinical evidence of hepatitis is rare in Q fever endocarditis. All of the 16 patients reported from Manchester and Edinburgh had evidence of liver involvement, and in one this led to death from cirrhosis. In fact, two patients presented primarily with liver disease. All but one of the patients had hepatomegaly and in many there was hepatic tenderness. Abnormal tests of liver function, particularly hyperglobulinemia, raised alkaline phosphatase and abnormal bromsulphthalein retention were found in all patients. Hepatic histology was abnormal in all eight patients in whom it was studied. Other workers have recorded isolation of *C. burneti* from hepatic tissue. These findings, coupled with thrombocytopenia which also occurs frequently, may help to differentiate Q fever endocarditis from bacterial endocarditis.

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Reply

To the Editor

We thank Dr Turck for his astute comments concerning our case report of Q fever endocarditis It has been of interest to us as to why this complication has been infrequently documented to occur in the United States In answer to Dr Turck s questions the initial serologic studies were not available before the patient died We agree that all of Koch s postulates were not fulfilled in this case However we believe the serologic studies as recorded strongly suggest *C burnetii* as the etiology of the infective endocarditis in our patient While it is true that phase I antibody in our patient was 1 32 as Dr Turck notes Ferguson and associates have reported the patient with Q fever endocarditis in whom the organism was isolated from the blood as well as the heart valves at autopsy in which this antibody titer was 1 64 Additionally the rise in phase II antibody in our patient suggests an active infective process In the absence of any pathologic evidence of hepatitis in our case we believe this serologic rise is even more indicative of active endocarditis due to *C burnetii* We agree with Dr Turck s recommendation that in the setting of a patient who has clinical signs and symptoms of infective endocarditis but whose blood cultures are persistently sterile that appropriate serologic studies be drawn including those for *C burnetii* and that treatment with tetracycline be seriously considered in addition to antibiotic therapy for more conventional organisms (i e *S fecalis* and anaerobes) we are in the process of surveying our geographic area to detect other unrecognized cases of endocarditis due to this organism

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Book reviews

Progress in Brain Research volume 47 Hypertension and *Brain Mechanisms* Edited by W DeJong A P Provoost and A P Shapiro Amsterdam 1977 Elsevier Scientific Publishing Company 437 pages Price $57 95

This book represents many papers presented at a workshop held in Utrecht during June 28 to 30 1975 The papers are grouped in accordance with the subjects discussed which included neuro anatomy and neurophysiological mechanisms of cardiovascular control neurotransmissions in relation to cardiovascular control brain damage and hypertension and pharmacologic aspects of antihypertensive agents. The many papers as a whole are excellent Furthermore this workshop emphasizes the brain and nervous system in pathophysiology and pharmacology as related to hypertension The contributors are from many parts of the world all actively engaged in studying hypertension Physiologists and pharmacologists especially should find this to be a useful book Clinicians would profit greatly by studying the many contributions This is a very good book and is highly recommended as a source of material on an aspect of hypertension which is too often ignored.

Practical Atlas of Cardiac Scintigraphy St. Louis Missouri, 1977 The C V Mosby Company 110 plates plus 21 page introduction Price $ .50

This atlas on cardiac scintigraphy is timely Interest in the use of nuclear medicine methods in *cardiology is increasing* rapidly This reviewer however finds the methods to offer very little useful service to clinical cardiology especially since the introduction of echocardiography Nuclear diagnostic procedures are expensive and increase further the already high cost of medicine Nevertheless, the *Atlas* in French and English does describe very well methodology and recommended clinical applications of nuclear scintigrams of the heart to cardiology The illustrations and legends are superb The colored plates are clear The practicing physician can determine for himself whether or not he would find these recordings useful in his practice And this excellent atlas does provide the reader with an opportunity to learn the principles of the methods, applications and indications of the methods as well as the results This is a fine atlas on a medical subject that is developing in popularity But the reader must decide for himself just how these nuclear procedures apply along with the clinical and electrocardiographic data Regardless the methods are being used fairly extensively and it therefore behooves the physicians to know when and how to employ them This book provides a good background for study

Basic Electrocardiography Handbook By Leonard J Lyon M D New York 1977 Van Nostrand Reinhold Company 175 pages. Price $11 95

This handbook of about 1 5 pages is intended for nurses paramedical assistants in hospitals and clinics and beginners in electrocardiography The book summarizes the approach used by the author in his teaching exercises The author has simplified many of the concepts in electrocardiography for nurses and paramedical personnel The book is intended to train people to recognize acute cardiac problems especially those related to arrhythmias Nurses and technicians will find this to be a very useful book on an important subject

Books received

ECG Diagnosis Self Assessment vol II By Edward K Chung, M D Hagerstown Md 19 Harper & Row Publishers, 444 pages Price $17 95

Mechanical Concepts in Cardiovascular and Pulmonary Physiology By Jerry Franklin Green Ph D Philadelphia 1977 Lea & Febiger Publishers 166 pages Price $10 00

Heart Disease in Infants Children and Adolescents 2nd ed Edited by Arthur J Moss Forrest H *Adams and George C* Emmanouilides Baltimore 1977 The Williams & Wilkins Company 57 pages. Price $ 00

Recent Advances in Studies on Cardiac Structure and Metabolism Vol 12 Cardiac *Adaptation* Edited by Tachio Kobayashi, Yoshi Ito and Georg Rona Baltimore London Tokyo 1978 University Park Press 751 pages Price $57 50

Recent Advances in Studies on Cardiac Structure and Metabolism Vol 11 Heart Function and Metabolism Edited by Tachio Kobayashi Toyomi Sano and Naranjan S Dhalla Baltimore London Tokyo 19 8 University *Park Press 638* pages Price $49.50

Symposium on Patient Education

The University of California San Francisco presents the second annual Symposium on Patient Education to be held in San Francisco on October 20 through 22 1978 Patient education is a process that involves a partnership between patients and members of the health care team This partnership has led to the development of this symposium in which persons who have had experience with disease and trauma will join with health professionals to learn about what is happening to their bodies and how to control the effects that their illness may have on their future lives This symposium has been designed to bring together key persons involved in these processes as a way to sustain the progress that has been achieved and to stimulate ideas and inquiries concerning patient education in the near future Fees for the symposium are Physicians—$90 (includes credit) General—$80 (includes credit) General—$70 (does not include credit) Full time students—$35 (letter of verification must accompany registration form) For registration information contact University of California San Francisco Continuing Education Health Sciences 1308 Third Ave San Francisco Ca 94143 Telephone (415) 666 2894

Advancement of Tension Control meeting

The fifth meeting of the American Association for the Advancement of Tension Control will be held on October 28 and 29 1978 at the Bismarck Hotel in Chicago Preceding the meeting will be a two day workshop conducted by Dr F J McGuigan on October 26 and 27 For information about the workshop and meeting please contact Dr F J McGuigan Executive Director AAATC P O Box 8005 Louisville Ky 40208

Pediatric and adolescent echocardiography course

The fourth annual Pediatric and Adolescent Echocardiography Course will be held on November 10 through 1[illegible] 1978 in Las Vegas, Nevada The course is sponsored by the American Society of Echocardiography American Institute of Ultrasound in Medicine and by H E I P For further information, please contact Pediatric Echocardiography Course 4340 Placita Panuco Tucson Ariz 85718 Telephone (60[illegible]) 88 6508

Lucien Dautrebande prize

The Foundation de Physiopathologie Professeur Lucien Dautrebande will award its next prize of approximately 900 000 Belgian francs during the year 1979 The award will be given to a study on human or animal clinical physiopathology such work preferably having therapeutic implications All applications for candidacy must be received by December 15 1978 For further information regarding the award and applications please write Office of the Foundation de Physiopathologie Professeur Lucien Dautrebande Chaussée de Liège 35 5200 Huy Belgium

American Heart Journal

November 1978 Volume 96 Number 5

Editorial

Coronary heart disease—the doctor s dilemma

George V Mann ScD MD*

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For 25 years the treatment dogma for coronary heart disease (CHD) has been a low cholesterol low fat polyunsaturated diet This treatment grew out of a reasonable hypothesis raised in 1950 by Gofman and others but soon a clot of agressive industrialists self interested foundations and selfish scientists turned this hypothesis into nutritional dogma which was widely impressed upon physicians and the general public A nadir was reached when zealous doctors and salesmen arranged such prudent meals for national meetings of cardiologists rather like Tupperware teas There grew up in the interface between science and the government funding agencies a club of devoted supporters of the dogma which controlled the funding of research a group known by the cynics among us as the heart Mafia Critics or disbelievers of the diet/heart dogma were seen as pariahs and they went unfunded while such extravagancies as the Diet/Heart trial the MRFIT trial and a dozen or more lavish Lipid Research Centers divided up the booty For a generation research on heart disease has been more political than scientific All this resulted from the abuse of scientific method A valid hypothesis was raised tested and found untenable But for selfish reasons it has not been abandoned T C Chamberlain the American geologist and philosopher described the situation succinctly in 1897 [1]

The moment one has offered an original explanation for a phenomenon which seems satisfactory that moment affection for his intellectual child springs into existence and as the explanation grows into a definite theory his parental affections cluster about his offspring and it grows more and more dear to him there springs up also unwittingly a pressing of the theory to make it fit the facts and a pressing of the facts to make them fit the theory

Since 1955 many examinations of the diet/heart hypothesis have shown that neither the level of serum lipids[2,3] nor the experience with CHD[4] can be related to dietary practice Clinical trials of prevention by diet both primary[5] and secondary[6,7] have shown that diet has no more than a trivial effect on cholesteremia and has no real effect on morbidity and mortality Two drugs niacin and atromid have larger effects than diet in lowering cholesteremia but they gave no health advantage[8,9]

Three drug treatments were abandoned because they caused an excess of disease in treated men These were estrogens at two levels[9] and dextrothyroxine The clinical trials do clearly show a doubling of the rate of cholelithiasis[12] and a questionable increase of cancer in subjects treated [1] It is not reasonable to say that while diets and drugs may not help they do no harm, they may indeed cause harm

This impasse creates two problems How is the public to be re educated? As a German journalist said I cannot tell my readers that the informa

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Recei ed fo p bli at on N v 2, 1977

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*Career I estig to (4-K06-HL-08288-16) from The N tional Heart Lung and Blood Inst tute.

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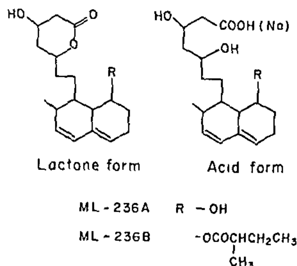


Fig 1 The factor derived from Penicillium cultures has recently been characterized by Endo and associates[17] This material is active both in vitro on the enzyme system which synthesizes cholesterol and in vivo The acid form *(right)* is more active than the lactone form Both contain the glutarate skeleton

tion I have been giving them about diet and heart disease over the past ten years is wrong that would destroy my credibility " Physicians have a similar problem with their patients But all of you, journalists and scientists, alike, had better recognize that the limb you are on is being sawed off

The doctor s dilemma would be eased if he had an effective substitute for the dietary dogma Partly because the diet/heart hypothesis has so usurped the research funds there is no established alternative—only some scattered unfunded ideas Physicians may be interested in some of these

There are two classes of causes of hypercholesteremia These are relevant because there is general agreement that cholesteremia is causally related in a curvilinear way to atherosclerotic disease The rare form affecting about one in 500 persons, is a genetic lesion of cell receptors[14] This lesion prevents the cholesterol in the low density lipoproteins from entering the cells and regulating the synthesis of cholesterol This is inherited as an autosomal recessive trait[15] Hypercholesteremia is present at birth in such persons and cardiovascular disease often but not always occurs prematurely There is no available treatment but there are three in the offing One is hydroxy methyl glutarate,[16] another is a material derived from Penicillium cultures[17] (Fig 1), and a third is a material called milk factor ' because it is found in milk[18] These materials offer promise of being of value in the control of synthesis of cholesterol and the prevention of premature vascular disease in this rare genetic disorder No presently available drugs or diets have been shown to do that

The common cause of cholesteremia appears to be an environmental agent which interferes with the catabolism of cholesterol to bile acid for excretion[19] The identity of this agent is not known, but there are several suspects These include the ' trans ' fatty acids produced by the hydrogenation of polyunsaturated oils, as in the manufacture of soft margarine [0] Human feeding trials show that trans fatty acids have a remarkable hypercholesteremic effect[21] Another suspect is carbon monoxide, which is known to interfere with the hydroxylating enzymes responsible for converting cholesterol to bile acid[22] Still another suspect is vitamin D, which since about 1940 has been added to many human foods and often in excessive amounts[23] Vitamin D in excess is an atherogenic agent in experimental animals

The role of high density lipoproteins in serum[24] of the cations in hard water and of fiber in food as protective agents against CHD is incompletely understood The fiber issue is clouded by bad epidemiological groundwork Burkitt should have read Bishop Berkeley more carefully before using un tended African populations as paragons of health 'To be is to be perceived

Physicians need to know, for their patients and for themselves what course to follow to minimize the risk of CHD A most impressive collection of evidence suggests that exercise and fitness protect from CHD [5] The disease is rare in physically active cultures[26] Men with exertional jobs[27] or men with sedentary jobs and exertional hobbies[28] have less trouble with CHD Maasai men who are exceptionally active, do have extensive atherosclerosis but with enlarged, ectatic vessels as they grow old so that the plaques are inconsequential[29] A clinical trial is needed to examine the role of exercise in the primary prevention of CHD Such a trial would be feasible because fitness measurements are available to measure compliance with the treatment Unhappily, and perhaps cynically, there is more money in soft margarine than in sneakers and athletic supporters

There was a saying in the Old West that you can t sell from an empty wagon ' Diet/heart has been a demonstration of that truism We need some solid evidence of the efficacy of exercise

before we mount a public health campaign In the meantime too many Americans are wearing the diet/heart hair shirt To borrow a phrase from Martin Luther King Let my people go

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Clinical communications

Adverse reactions to methyldopa with particular reference to hypotension

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Methyldopa is widely used in the treatment of all forms of hypertension After an initial period in which it was thought to act by inhibiting dopa decarboxylase in sympathetic nerves it is now generally accepted to mediate its effect by a direct action on the brain [1]

Side effects from this drug are often troublesome Johnson and colleagues[2] reported their occurrence in 72 per cent of recipients, the major problems being weight gain and drowsiness occurring during long term therapy Subsequently Pritchard and associates[3] reported that 20 per cent of patients receiving this drug had to discontinue treatment because of side effects The majority of reported side effects appear to be dose related,[4] leading to the suggestion that an upper limit of 3 grams should be placed on the daily dose of methyldopa [5]

The present report provides details of the adverse effects of methyldopa as seen in a large comprehensive drug surveillance program which monitors consecutive admissions to medical wards in university teaching hospitals In particular the information available on the occurrence of hypotension during methyldopa therapy is analyzed in depth

Patients and methods

The Boston Collaborative Drug Surveillance Program uses nurse monitors to collect information on consecutive admissions to medical wards in teaching hospitals in participating centers in seven countries The information obtained includes routine demographic details, a history of past medication use, together with precise details of all medications prescribed during the patients stay in hospital Data collected include dose route frequency, starting and stopping indications for the drug Where a patient develops any undesired or unintended effects attributed to the drug, a detailed evaluation of the effect is undertaken by the attending physician and a clinical pharmacologist For the present report only those adverse effects deemed to be 'definitely or 'probably due to methyldopa are included A record is kept of the results of certain routine laboratory tests taken on admission and up to four discharge diagnoses Greater details of the

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Received for publication Nov 9 1977

Accepted for publication Jan 16 1978

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The Boston Collaborative Drug Surveillance Program has been supported by the National Institute of General Medical Sciences (Grant No 1 R01 GM23430 01) and in part by grants from the United States Food and Drug Administration (Grant No 1 R01 FD00920 01) the Canadian Health Protection Branch the Israeli Ministry of Health the Hadassah Medical Organisation the Kupat Holim Auckland Hospital Auckland New Zealand Roger Williams General Hospital (Brown University N I G M S Grant No GM 165 39-02) and the Scottish Home and Health Department The hospitals which have participated in the ongoing part of the Boston Collaborative Drug Surveillance Program are Boston Massachusetts–Lemuel Shattuck Hospital Peter Bent Brigham Hospital Boston City Hospital Veterans Administration Hospital Massachusetts General Hospital and University Hospital Providence Rhode Island–Roger Williams General Hospital Syracuse New York–State University Hospital of the Upstate Medical Center Tucson Arizona–Arizona Medical Center Richmond Virginia–Virginia Commonwealth University Hospital Canada–St Joseph's Hospital London Ontario Israel–Hadassah Hebrew University Hospital Jerusalem Beilinson Medical Center Petah Tiqva Asaf Harote Hospital Zerifin and Rambam University Hospital Haifa New Zealand Auckland Hospital Auckland and Hutt Hospital Wellington Scotland–Western Infirmary and Stobhill General Hospital Glasgow Italy–Desio Hospital Milan West Germany–Klinikum Steglitz der Frei Universitat Berlin

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exact methodology employed have been published elsewhere[6,7]

This report is based on information collected between 1966 and 1975 on 26 294 consecutive hospitalized patients in 21 hospitals in the U S Canada Israel New Zealand Scotland Italy and Germany of whom 1 067 (4 per cent) received methyldopa during their first monitored admission to the study

Results

The mean age of the 1 067 methyldopa recipients was 57 years 52 per cent were males and 3 5 per cent died during the monitored admission The primary discharge diagnosis was of cardiovascular disease in 616 patients (58 per cent) renal disease in 99 (9 per cent) respiratory disease in 75 (7 per cent) endocrine disease in 66 (6 per cent) A variety of other conditions made up the remaining 20 per cent of diagnoses A history of previous drug treatment was available for 952 (89 per cent) patients Of these 275 (29 per cent) had not previously received hypotensive therapy The sole indication for methyldopa treatment was hypertension The mean diastolic blood pressure of the 275 newly diagnosed hypertensive patients was 116 (SEM 1 3) mm Hg on admission as compared to 10[illegible] (SEM 0 9) mm Hg for those who had received previous hypotensive therapy

Adverse effects were attributed to methyldopa in 149 patients (14 per cent) The most frequent reaction was excessive hypotension which was reported in 110 patients (10 3 per cent) and was often noted to be postural In the majority of patients where the actual pressure was recorded the systolic value was below 100 mm Hg or the diastolic below 70 mm Hg (see Discussion section) Other reactions included drowsiness hematological upsets cutaneous manifestations and upset in libido Details of the reported frequency of these events is given in Table I

Extrapyramidal signs and hemolytic anemia were reported in six patients who had a history of methyldopa use prior to hospitalization and responded gradually to withdrawal of the drug Rise in blood urea nitrogen levels occurred in two patients both of whom also suffered from significant hypotension Bradycardias of 36 beats/minute and 42 beats/minute respectively were recorded in two patients shortly after commencing methyldopa In one of these patients 250 mg was given orally and in the other 250 mg was given intravenously Bradycardia responded to reduction in the frequency of administration of the drug in both instances Methyldopa related pyrexia was reported in two patients and again responded completely to withdrawal of the drug

Table I Adverse effects attributed to methyldopa

	Number of patients	*Per cent*
Hypotension	110	10 3
Drowsiness	26	2 4
Depression	5	0 5
Extrapyramidal signs	4	0 4
Gastrointestinal upsets	4	0 4
Headaches	2	0 2
Cutaneous manifestations	2	0 2
Hemolytic anemia	2	0 2
Drug related fever	2	0 2
Bradycardia	2	0 2
Rise in blood urea nitrogen levels	2	0 2
Alteration in liver function	1	0 1
Disturbance in libido	1	0 1

A patient may have more than one adverse effect attributed to methyldopa.

Adverse effects of methyldopa were judged by the attending physicians to have been life threatening in nine instances Details of these patients are given in Table II Six of these nine patients suffered from cerebral or cardiac ischemic episodes while receiving methyldopa None died as a result of the adverse reaction

For the purpose of further analyses designed to explore the relationships between toxicity and various patient and drug related factors patients were classified into three categories according to the presence of hypotension related to methyldopa other adverse effects of the drug or no adverse effects Patients suffering from more than one adverse effect were preferentially assigned to the hypotension category if this was one of the reported effects

Hypotension related to methyldopa usually occurred early during treatment over two thirds of the reported episodes occurring within four days of starting treatment although some were reported as late as the 36th day of treatment (Fig 1) The most common time for methyldopa related hypotension to be observed was between 24 and 72 hours after commencing treatment

The frequency of all adverse effects (both

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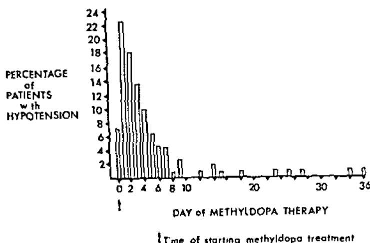


Fig 1 Duration of methyldopa treatment in relation to occurrence of hypotension

hypotension was real or due to confounding by age and/or dose The results showed that the frequency of methyldopa attributed hypotension was indeed related to diastolic blood pressure independently of both age and daily dose (Table VII)

Adverse reactions were not significantly related to sex survival, admission serum albumin levels a past history of methyldopa or of diuretic therapy or concurrent treatment with diuretics No attempts were made to consider the effects of prior hypotensive therapy with agents other than diuretics or methyldopa since the available information indicated that this was an extremely complex matter likely to be evaluated satisfactorily only in a clinical trial situation or if greater number of patients were available for study by the present methods.

There was an apparent relationship between admission hematocrit levels and methyldopa toxicity The mean hematocrit of patients with hypotension attributed to methyldopa was 37 9 (SEM 0 8) per cent as compared to 40 (SEM 0 3) per cent for those with no adverse reactions However there was an extremely strong relationship between admission blood urea nitrogen levels and hematocrit Thus whereas 74 per cent of patients with hematocrits greater than 40 per cent had admission BUN levels below 25 mg per cent only 19 per cent of those with hematocrits below 34 per cent were in this group Similarly whereas only 4 per cent of those with hematocrits greater than 40 per cent had admission BUN levels above 50 mg per 100 ml 57 per cent of those with hematocrits below 34 per cent were in this group

When this confounding relationship between hematocrit and BUN was taken into account the relationship between hematocrit and methyldopa toxicity disappeared

Discussion

In this study an adverse reaction is defined as any undesired or unintended effect attributed to a drug by an attending physician No strict definitions of events such as drug attributed hypotension were given to the contributing centers Nevertheless in practice where an accurate record of the patient s blood pressure was given it was usually lower than a systolic of 100 mm Hg or diastolic of 70 mm Hg unless the patient complained of symptoms referable to a sudden drop in pressure when even a recording of 120/80 mm Hg may have been deemed undesirable By contrast some patients may have experienced unrecognized episodes of hypotension If these were not associated with symptoms which led the staff to actually record their blood pressure such patients would go unrecorded in this program In practice the group of patients studied is one in which a clinically significant fall in blood pressure was recorded and attributed to methyldopa treatment

The frequency of hypotension was positively related to admission blood urea nitrogen levels and to daily dose of methyldopa and was negatively related to age and to weight When the combined effects of these variables was taken into account by multiple stratification all were found to be significant factors in predicting hypotension Thus for example the risk of hypotension was 3 per cent in patients over the age of 55 years

Table II Life threatening reactions attributed to methyldopa

Patient	Age/sex	Diagnosis	Methyldopa daily dose (mg)	Total dose (mg)	Route	Time → AR(d)	Comment	Physician's assessment*
1	76/F	Hypertensive heart disease renal failure diabetes mellitus	750	1 500	P O	2	Developed severe sinus bradycardia and hypotension (70/40) after two days treatment recovered in 3 days	P
2	46/M	Acute myocardial infarction	750	750	P O	1	Developed severe chest pain and became hypotensive after three 250 mg tabs methyldopa Recovered	P
3	59/M	Chronic glomerulonephritis	500	2 500	P O	5	Hypotension (80/40) and marked drowsiness Responded to withdrawal of methyldopa	P
4	61/M	Hypertension arteriosclerosis	1 000	1 000	P O	1	Transient left sided weakness and dysarthria Recovered completely in few days	P
5	43/M	Hypertension nephrosclerosis	1 000	6 000	P O	6	Developed postural hypotension (100/60) accompanied by severe chest pain Recovered without permanent cardiac damage	D
6	39/M	Subarachnoid hemorrhage hypertension	3 000	3 000	P O	1	After methyldopa and pethidine 75 mg I V became shocked (65/50) drowsy confused and dysarthric for three days Recovered without sequelae	D
7	42/M	Hypertension diabetes mellitus	2 000	2 000	P O	1	Became hypotensive (70/40) vomited and developed right hemiparesis which failed to respond to treatment	D
8	45/F	Essential hypertension gastric ulcer	2 000	2 000	I V	1	Found disorientated with hypotension (80/60) and extrapyramidal symptoms Recovered after receiving metaraminol I V infusion	D
9	48/M	Chronic pyelonephritis hypertension	500	500	P O	1	After receiving second dose of methyldopa developed transient left hemiparesis B P not recorded	D

P = drug probably caused reaction D = drug definitely caused reaction

hypotension and others) was related to duration of hospitalization some 11 6 per cent of 880 patients hospitalized for up to 19 days having a reported adverse effect as compared to 25 per cent of 187 patients hospitalized for more than 20 days ($X_1 = 25$, $p < 0\ 01$) The mean duration of hospitalization among reactors was 17 3 (SEM 1 5) days and among non reactors 12 5 (SEM 0 4) days

The frequency of hypotension, but not of the other adverse effects was significantly related to age, blood urea nitrogen concentration (BUN) on admission to hospital weight, daily dose of methyldopa, and admission diastolic blood pressure (Table III) There was a strong correlation between age and admission diastolic blood pressure both for the 677 patients who gave a history of taking hypotensive therapy before admission and for the 275 patients who did not take such therapy

Detailed analysis undertaken to elucidate interactive effects between age, BUN levels and dose in the generation of hypotension showed that the effects of age and of daily dose were present within various strata of BUN levels both separately (Table IV) and together (Table V) Similar analyses to seek interactive effects between weight BUN and (separately) age and daily dose of methyldopa showed the effects of age and of daily dose to be present both in light and in heavy subjects and to be most marked in those with admission BUN levels below 25 mg/100 ml By contrast, in patients with elevated admission BUN levels the effect of weight on the frequency of hypotension was largely obscured by those of age and daily dose of methyldopa (Table VI)

Similarly detailed analyses were undertaken to determine whether the apparent effect of admission diastolic blood pressure on the frequency of

Table IV Frequency of hypotension in relation to admission blood urea nitrogen levels * age and daily dose (separately)

	Blood urea nitrogen (mg /100 ml)							
	0-24		25-49		50+		Total	
	No	%	No	%	No	%	No	%
Age (years)								
<49	19/18	= 10 4	14/45	= 31 1	20/83	= 24 1	53/310	= 17 1
50-69	?1/310	= 6 8	9/118	= 7 6	12/?9	= 15.2	42/507	= 8 3
?0+	5/115	= 4 4	6/69	= 8 7	2/14	= 14 3	13/198	= 6 6
Daily dose (G)								
<1	19/396	= 4 8	11/139	= 7.9	13/101	= 12 9	43/636	= 6 8
1 19	17/154	= 11 0	6/59	= 10 2	14/57	= 24 6	37/270	= 13 7
2+	9/57	= 15 8	12/34	= 35 3	7/18	= 38 9	28/109	= 25 7

In 5 patients (4 8 per cent) the admission blood urea nitrogen level was not recorded

per cent of recipients in this series This is less than has been reported by other workers [1] and is likely to be a substantial underestimate of the true frequency in part because drowsiness is less troublesome and indeed less noticeable in hospitalized patients as compared to ambulant subjects and in part because hospitalized patients may receive a wide variety of other drugs which can cause drowsiness and hence be incriminated in preference to methyldopa Likewise depression which has been reported during methyldopa therapy [3] could be under recorded in the present study

Extrapyramidal signs following treatment with methyldopa have been recorded by some workers[1 6] and are presumably due to inhibition of the dopa decarboxylase in the brain In the present series only four patients (0 4 per cent) manifested clinically significant Parkinsonism

Gastrointestinal upsets were rare following methyldopa therapy as were rashes Moreover a detailed analysis of the entire Boston Collaborative Drug Surveillance Program data base failed to reveal any allergic reactions which could have been due to methyldopa which went unrecognized by the attending physicians

Hemolytic anemia consequent upon methyldopa use has been well documented [9] and occurred in two patients in the present series both of whom had received the drug prior to hospitalization No information is available on the prevalence of positive Coombs tests in the current series of patients although the expected frequency appears to be between 5 and 30 per cent of long term users

Table V Frequency of hypotension in relation to admission blood urea levels age and daily dose of methyldopa

Daily dose (G)	Age (years)	Admission Blood Urea Nitrogen levels (mg /100 ml) 0 25 No	%	25+ No	%	Total No	%
≤1	≤55	11/145	7 6	13/95	13 7	?4/240	10 0
	55+	8/251	3 2	11/145	7 6	19/396	4 8
1+	≤55	15/113	13.3	25/ 9	31 6	40/192	20 8
	55+	11/98	11 2	14/89	15 7	25/187	13 4

Methyldopa related fever has been reported previously[20] and was observed in two patients in this study In one further patient mild pyrexia associated with alteration in liver function test results was attributed to methyldopa This drug has been suspected of causing liver damage for some time [2 23] and although it appears to be a rare complication drug induced hepatitis should be kept in mind as a possible cause of upset liver function in such patients

Clinically significant bradycardia is rare after therapy with methyldopa and was reported in only two patients in the present series

Disturbance in libido is a common complication of hypotensive therapy more so with the ganglion blocking drugs guanethidine and bethanidine than with methyldopa Nevertheless it is rarely reported voluntarily to medical attendants[1] and is likely to be least troublesome in a group of hospitalized patients[1] The fact that one patient in this study who had received the drug

Table III Factors predicting methyldopa toxicity

	Frequency of hypotension (%)	*Frequency of other reactions (%)*
Age		
Less than 50 years	54/321 = 16 8	12/321 = 3 7
50 59 years	23/272 = 8 5	9/272 = 3 3
60 69 years	19/261 = 7 3	10/261 = 3 8
70+ years	14/213 = 6 6	8/213 = 3 8
Blood urea nitrogen*		
Less than 25 mg /100 ml	45/607 = 7 4	20/607 = 3 3
25-49 mg /100 ml	29/232 = 12 5	10/232 = 4 3
50+ mg /100 ml	34/176 = 19 3	8/176 = 4 5
Weight†		
Less than 150 lb	44/321 = 13 7	18/321 = 5 6
150-174 lb	22/229 = 9 6	8/229 = 3 5
175+ lb	26/302 = 8 6	8/302 = 2 6
Daily dose		
Less than 1 G	44/660 = 6 7	16/660 = 2 4
1 1 9 G	38/280 = 13 6	18/280 = 6 4
2 2 9 G	18/70 = 25 7	3/70 = 4 3
3+ G	10/57 = 17 5	2/57 = 3 5
Admission diastolic blood pressure‡		
Less than 105 mm Hg	36/494 = 7 3	16/494 = 3 3
106 115 mm Hg	16/188 = 8 5	7/188 = 3 7
115+ mm Hg	58/380 = 15 3	16/380 = 4 2

*Value not recorded in 52 patients (4.8%)
†Value not recorded in 215 patients (20%)
‡Value not recorded in 5 patients (0 5%)

who had admission blood urea nitrogen levels below 25 mg per 100 ml and were given up to one gram of methyldopa daily By contrast the risk was increased tenfold (to 32 per cent) among patients aged 55 years or less whose admission BUN level was greater than 25 mg per 100 ml and who received more than one gram of methyl dopa daily

Similarly, the risk of hypotension was 3 per cent in heavy subjects over the age of 55 years who had normal BUN levels on admission as compared to 24 per cent in lighter, younger subjects with elevated admission BUN levels In heavy subjects with normal BUN levels receiving up to 1 gram methyldopa daily, the frequency of hypotension was 3 per cent, whereas in light subjects with elevated BUN levels receiving more than 1 gram daily, the comparable frequency was 24 per cent

The relationship between dose and hypotension is readily explicable and has previously been noted by other workers including Smirk[4] who observed a large inter individual variation in the dose necessary to produce hypotension Methyl dopa is known to be excreted in part in the urine and to be retained in the body in patients with renal failure,[8] thus the relationship between increasing effect and increasing impairment of renal function as manifest by elevated admission BUN levels is also readily explicable Similarly the effect of patient weight can be explained on a pharmacological basis The effect of age which was observed independently of dose weight diastolic blood pressure, and BUN concentration is less readily explicable on a pharmacological basis It is unlikely to be due to observational differences between young and old patients since there was a gradual increase in the frequency of hypotension with decreasing age at all dose levels examined and this was present in both light and heavy patients in those with mild and those with severe hypertension, and in those with normal and elevated BUN levels The most likely explanation of this finding is that hypertension occurring in younger patients is more labile than in the elderly, and hence more prone to fall after a given stimulus than in elderly subjects Whatever the explanation, the finding is impressive since there was a threefold difference in the frequency of reported hypotension at all dose levels in the young relative to the elderly patients

An initial association between hematocrit and hypotension appeared impressive insofar as patients with an admission hematocrit of less than 30 per cent had a twofold greater prevalence of methyldopa related hypotension than did those with hematocrits above 45 per cent Nevertheless this difference was almost entirely a reflection of severity of renal impairment rather than any effect of anemia on the kinetics of methyldopa per se—a possibility which deserved careful consideration in a drug which may produce hemolytic anemia[9] particularly since anemia has been shown to significantly alter the pharmacokinetic handling of other drugs such as gentamicin[10] Neither hypotension nor the other adverse effects of methyldopa were related to sex admission serum albumin levels previous exposure to methyldopa or diuretic drugs, or current exposure to diuretics Moreover, the other adverse effects (predominantly drowsiness) were unrelated to age weight daily dose of methyldopa and only marginally related to admission BUN levels

Drowsiness was reported in only two and a half

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Table VI Frequency of hypotension in relation to admission blood urea levels, age, weight, and daily dose of methyldopa

	Weight*	Admission blood urea nitrogen levels (mg /100 ml) 0 25		25+		Total	
		No	%	No	%	No	%
Age (years)							
≤55	≤150	10/56	17 6	15/62	24 2	25/118	21 2
55+		9/107	8 4	9/84	10 7	18/191	9 4
≤55	150+	14/161	8 7	18/86	20 9	32/247	13 0
55+		5/160	3 1	10/93	10 8	15/253	5 9
Daily dose (G)							
≤1	≤150	10/113	8 8	8/80	10	18/193	9 3
1+		9/50	18 0	16/66	24 2	25/116	21 6
≤1	150+	6/204	2 9	11/106	10 4	17/310	5 5
1+		13/117	11 1	17/73	23 3	30/190	15 8

Value not recorded in 215 patients (20 per cent)

Table VII Frequency of hypotension in relation to age admission diastolic blood pressure and daily dose of methyldopa

Admission diastolic B P (mm Hg)	Daily dose (G)	Age (years) ≤ 55		55+		Total	
		No	%	No	%	No	%
≤ 110	≤ 1	8/112	7 1	8/228	3 5	16/340	4 7
	1+	10/63	15 9	12/99	12 1	22/162	13 6
110+	≤ 1	16/137	11 7	12/180	6 7	28/317	8 8
	1+	31/138	22 5	13/105	12 4	44/243	18 1

Value not recorded in 5 patients (0 5 per cent)

prior to hospitalization was reported to suffer from this side effect dose not give an accurate picture of its prevalence in the outpatient setting

The present survey of over 1 000 consecutive recipients of methyldopa indicates that to minimize the risk of hypotension, therapy with this drug should be initiated cautiously especially in younger patients in the non obese in those presenting with severe hypertension, and in those with impairment of renal function as manifest by raised BUN levels on admission

Summary

Of 26 294 consecutive patients monitored in a comprehensive drug surveillance program, 1067 (4 per cent) received methyldopa for treatment of hypertension Adverse reactions attributed to methyldopa were reported in 149 patients (14 per cent), the most frequent being hypotension Life threatening adverse effects were reported in nine patients (6 per cent of reactors)—the major problems being hypotension associated in several patients with signs of cardiac or cerebral ischemia Hypotension attributed to methyldopa was more frequent in younger patients in those with uremia in lighter subjects and in those receiving a high daily dose Marked interaction between these factors was demonstrated and eightfold differences in the frequency of hypotension were observed in different sub groups of methyldopa recipients Adverse effects other than hypotension were reported infrequently and did not correlate well with the previously mentioned factors

The findings suggest that methyldopa therapy should be commenced cautiously in younger patients in the non obese, and in those with impairment of renal function as manifest by elevated blood urea nitrogen levels

range of normal venous oxygen saturations were depressed and there was a step up in oxygen saturation in the right atrium During the latter part of the procedure the oxygen saturations became increased and were similar in both ventricles, in the pulmonary artery and in the ascending aorta Pulmonary arterial systolic pressure was 30 mm Hg higher than aortic systolic pressure Cineangiocardiograms revealed bidirectional shunting at the atrial level shunting from the pulmonary artery to the aorta via a large ductus arteriosus and persistent filling of pulmonary veins for 9 seconds after the pulmonary artery injection Neither the left atrium nor other channels of venous drainage opacified The diagnosis was pulmonary venous obstruction probably due to common pulmonary vein atresia The infant was maintained on a respirator with 100 per cent oxygen but he developed severe bradycardia and died nine hours later

Autopsy findings

GROSS The lungs were normally located and well aerated The pericardial sac contained a small amount of clear yellow fluid The heart examined with the lungs intact was slightly enlarged but the external configuration was not otherwise remarkable The right atrium and right ventricle were normal A patent ductus arteriosus measuring 3 mm in diameter arose from the pulmonary artery of the same size and communicated with the distal segment of the aortic arch Two pulmonary veins drained each lung and formed a common thin walled channel of 2 mm internal diameter which ended blindly near the right atrial wall No accessory pulmonary veins were identified Radiographic examination with contrast injection confirmed that the small channel formed a cul de sac and did not connect with either the right or left atrium and that there was no other connection of pulmonary veins The left atrium was abnormally small and the mitral valve the left ventricle and the aorta were normal

MICROSCOPIC Significant microscopic findings were found only in the lungs Pulmonary tissue was mature but with the alveolar spaces incompletely expanded and some areas revealed atelectasis and capillary congestion There were no areas of inflammation or hyaline membrane The lymphatic vessels were dilated but apparently only to the extent as is usually seen in the lungs of stillborn infants



Fig 1a Chest radiograph. Case 1 See text for description

Case 2 A 3 4 kilogram boy was delivered normally after a 44 week uncomplicated pregnancy to a quadrigravid quadriparous 33 year old woman A first cousin had died with complete transposition of the great arteries A nuchal cord was present Apgar scores on the infant were 7 at one minute and 10 at three minutes No resuscitative measures were necessary however at eight minutes the infant quickly became cyanotic and cyanosis persisted despite oxygen therapy At age two days he was admitted to the intensive care nursery by transfer from another hospital Despite oxygen and bicarbonate therapy arterial blood gases on admission were pH 7 14 PO_2 38 mm Hg and base excess --16

The baby appeared moribund with flaccidity, nasal flaring and grunting respirations at a rate of 84 per minute There was diffuse cyanosis however the head and face were purple secondary to the nuchal cord The precordium was overactive the first and second sounds were single and a murmur was not audible All peripheral pulses were bounding in type and the liver edge was 3 cm below the right costal margin

The chest roentgenogram revealed a bell configuration pulmonary vascular congestion with mild hyperaeration and a normal heart size (Fig 1 *b*) The electrocardiogram was abnormal signs of right ventricular hypertrophy included a QRS axis of 165 degrees a high voltage qR pattern in Lead V_1 and an rS ratio in Lead V_6 of 0 4

The infant was digitalized intravenous infusions of dextrose water and sodium bicarbonate were continued An abbreviated cardiac catheterization was performed (Table I) he was resusci

Common pulmonary vein atresia

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Atresia of the common pulmonary vein (CPVA) occurs rarely, to our knowledge this condition has been previously reported in only eleven infants [1-6]. The number of cases is larger if one includes those having a minor accessory pulmonary vein which drains into the systemic circulation [7, 8]. Two additional babies with a premortem diagnosis of isolated CPVA, and a third example of CPVA associated with the asplenia syndrome and other cardiac anomalies form the basis of this report. One baby had histological evidence of acute pericarditis, probably a fortuitous perinatal event unrelated to pathogenesis of the cardiac anomaly. These three infants had been admitted to the Intensive Care Nursery of St Marys Hospital Medical Center, Madison Wisconsin where they underwent cardiac catheterization, and subsequently postmortem examination.

This report emphasizes (1) the developmental relationship of the pulmonary and bronchial venous circulations together with the manner in which the collateral circulation may help to sustain life for a brief period (2) clinical and laboratory features upon which the diagnosis of atresia of the common pulmonary vein may be based, and (3) clinical implications of pathophysiology which must be considered so that diagnostic, medical, and surgical measures may be pursued. Despite the fact that our patients and all other reported infants with atresia of the common pulmonary vein have not survived, a successful result of medical and surgical treatment is considered feasible.

Case reports

Case 1 A 24 hour term son of a 19 year old primigravid mother weighed 3 2 kilograms when admitted to the intensive care nursery from a nearby hospital. The gestational history had been uneventful. The one minute Apgar score of 9 had declined to 5 at the five minute evaluation. Cyanosis and distressed breathing had persisted since shortly after birth. Aspiration of a profuse amount of mucus from the airways and ventilation with 100 per cent oxygen did not diminish the cyanosis. The chest had a wide anterior–posterior diameter. Respirations were shallow at a rate of 88 per minute. The heart rate was 165 per minute, both heart sounds were loud and single without murmurs. The peripheral pulses were normal and the liver was not palpable.

Initial arterial blood gases with the infant breathing 100 per cent oxygen on the respirator were pH 7 19, PO_2 13 mm, and PCO_2 52 mm Hg. Dextrose water and bicarbonate were administered intravenously. The electrocardiogram was abnormal for age 24 hours with evidence of right ventricular hypertrophy, the QRS axis was deviated far rightward to 180 degrees, a high voltage QR pattern occurred in Lead V_1, and the rS ratio in V_6 was 0 7. The chest roentgenogram revealed diffuse pulmonary congestion with an indistinct cardiac border (Fig 1 *a*).

Cardiac catheterization was performed while the infant breathed 100 per cent oxygen in a vinyl hood (Table I). Venous pressure was at the upper

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Received for publication Nov 11 1977

Accepted for publication Jan 16 1978

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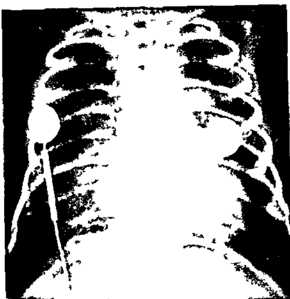


Fig 1b Chest radiograph Case 2 See text for description

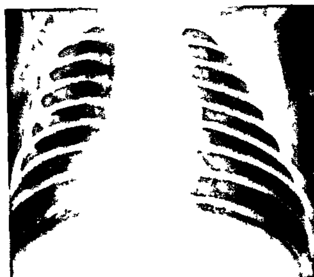


Fig 1c Chest radiograph Case 3 See text for description

ry pulmonary veins were present Bronchial vessels were identified but were not abnormally prominent and communicated normally

MICROSCOPIC Evidence of an active pericarditis was a conspicuous feature The serosa was thickened edematous and infiltrated with numerous polymorphonuclear leukocytes and lesser numbers of eosinophils and lymphocytes Some of the sections revealed a small amount of granular lipid material associated with this inflammatory lesion The infiltrate was confined to the outer aspects of the myocardium and did not involve the endocardium at any point Special stains for lipid infiltration of the heart and for fungi and bacteria were negative The blebs noted over the external surfaces of the lungs were dilated lymphatic vessels

Case 3 A 3 9 kilogram girl was delivered uneventfully to a primigravid 19 year old mother after an uncomplicated 40 week gestation The one minute Apgar score was 8 and the five minute score was 9 At three hours the baby became cyanotic The heart sounds were most prominent in the right hemithorax the first and second sounds were single and a murmur was not audible Roentgenograms (Fig 1 c) revealed dextrocardia and indistinct cardiac borders but not severe pulmonary congestion Many Howell-Jolly bodies were seen in the peripheral blood smear The electrocardiogram was compatible with mirror image inversion of the atria and sinus rhythm High voltage RS complexes in right precordial leads and a QR configuration from Leads V through V indicated right ventricular hypertrophy The findings were diagnostic for the asplenia syndrome

Cardiac catheterization was performed while the baby breathed 100 per cent oxygen (Table I) The inferior vena cava joined the cardiac silhouette at the usual location in the right paravertebral area and there was a left superior vena cava The right atrium in a mid heart location was arterialized Right ventricular and aortic systolic pressures were equal A dilated right ventricle on the right heart border gave origin to a large transposed aorta in the levoposition Pulmonary arteries smaller than the aorta were filled only from a patent ductus arteriosus Pulmonary venous drainage was not identified although cine filming was continued for 4 5 seconds after the pulmonary arteries opacified At nine days a Blalock shunt was performed with anastomosis of the right subclavian artery to the right pulmonary artery but the baby was not improved and died the following day

Autopsy findings

GROSS The spleen was absent The cardiac atria were inverted with the limbus of the fossa ovale identified in the left sided chamber Anomalies consisted of a large atrial septal defect of the ostium secundum type a dilated and heavily trabeculated single anatomic right ventricle

Table I Cardiac catheterization

Site	Case 1 (age 1 day)†				Case 2 (age 3 days)†				Case 3 (age 2 days)†			
	PH	Oxygen saturation %	Pressure (mm Hg)		PH	Oxygen saturation %	Pressure (mm Hg)		PH	Oxygen saturation %	Pressure (mm Hg)	
			S/D*	Mean			S/D*	Mean			S/D	Mean
SVC	7 30	53	6/1	3	–	–	–	–	7 44	59	3/0	1
IVC	–	55	6/4	5	–	–	–	–	–	69	4/2	3
RA	–	70	7/3	5	6 83	19	16/9	12	–	84	5/0	[illegible]
LA	7 32	60	8/0	4	6 95	27	21/12	16	–	–	–	–
RV	–	61 88‡	88/0	–	–	21	62/0	e d = 12	–	82	87/0	e d = 5
LV	7.33	89‡	62/0	–	7 12	32	–	–	–	–	–	–
PA	–	91‡	87/27	65	–	–	–	–	–	–	–	–
Ao	7 33	93‡	54/34	46	–	–	39/25	–	7 40	79	88/57	70

Abbreviations S/D = Systolic diastolic e d = end diastolic
†All infants breathed 100 per cent oxygen Cases 1 and 3 by a vinyl hood and Case 2 by a respirator
‡Saturations were obtained near the end of procedure
All peak venous pulses were a waves

Table II Clinical features of common pulmonary vein atresia

History & physical examination
1 Usually term infants
2 Immediate condition at birth may be good
3 Cyanosis and distressed breathing ensue quickly
4 No cardiac murmur
5 Severe acidosis
6 Congestive heart failure
Electrocardiogram
Right ventricular hypertrophy
Roentgenogram
1 Heart size normal border may be indi tinct
2 Severe pulmonary congestion
Cardiac Catheterization
1 Oxygen saturation low and similar in all chambers
2 Pulmonary artery pressure suprasystemic
3 Elevated venous pressure
Angiocardiogram
1 Right to left shunting via foramen ovale and ductus arteriosus
2 Pulmonary veins opacify but not other structures of venous drainage

tated throughout breathing 100 per cent oxygen via an endotracheal tube on a respirator Venous pressure was severely elevated and blood in all chambers was hypoxemic He was hypotensive right ventricular systolic pressure exceeded aortic pressure Cineangiocardiograms in the right and left atria and right ventricle revealed bidirection al shunting across the atrial septum tricuspid regurgitation, filling of the descending aorta from the pulmonary artery via a large ductus arterio sus, a small left atrium, and a small left ventricle Pulmonary veins opacified distinctly behind the heart, but continued filming for 6 5 seconds revealed no opacification of the left atrium or any anomalous venous channels The diagnosis was common pulmonary vein atresia Surgical correc tion was planned but he died three hours later

Autopsy findings

GROSS Both lungs were moderately emphysem atous and blebs were seen over the external surfaces The left lung was partially collapsed There was no excess of pleural fluid The pericar dial sac contained 5 ml of blood tinged fluid The epicardial surface was smooth and glistening without abnormal openings or hemorrhage The heart chambers and arteries were normally oriented A huge pulmonary artery arose from a dilated and hypertrophied right ventricle The aortic arch was approximately one third the size of the pulmonary artery and the aortic isthmus was hypoplastic The ductus arteriosus was approximately equal in size to the pulmonary artery and communicated with a large descending aorta An oval atrial septal defect just above a normal foramen ovale measured 2 × 1 cm The tricuspid valve was structurally normal but dilated The left atrium and left ventricle were small Small pulmonary veins drained all lobes of the lungs but did not join the left atrium at any point They formed a closed tube like blind venous chamber measuring 3 × 1 cm No accesso

such as occurs in the tetralogy of Fallot Conversely the pulmonary circulation is engorged and the arterial pressure is elevated to a suprasystemic level when obstruction occurs beyond the pulmonary capillary bed as in CPVA and TACPV with obstruction Histologic evidence indicates that there can be retrograde flow of capillary blood into the pulmonary arteries when the pulmonary veins are totally occluded Wagenvoort and colleagues[14] described dilated bronchopulmonary arteries and bronchopulmonary venous anastomoses in cases of aortic atresia with prematurely closed foramen ovale a condition hemodynamically similar to CPVA Marchand and associates found that the bronchial arteries in the full term fetal lung and in the atelectatic lung of the stillborn infant have a calibre nearly equal to that of adult vessels Since the direction of flow in bronchopulmonary arterial anastomoses will depend upon the pressure relationship in the pulmonary and bronchial arteries pulmonary capillary blood may enter the systemic circulation via bronchial arteries as well as bronchial veins

The basis for clinical and laboratory features of CPVA Cardiorespiratory function is severely altered immediately after birth in infants with CPVA and causes their early death Thus it is urgent to establish the diagnosis quickly Clinical and laboratory findings are summarized in Table II Obstructed pulmonary venous drainage may be suspected in infants who do not require resuscitation at birth but who quickly develop cyanosis and severe respiratory distress They have electrocardiographic evidence of right ventricular hypertrophy The roentgenographic appearance of severe pulmonary congestion is similar in CPVA TACPV with obstruction and idiopathic pulmonary lymphangiectasis The heart size is normal radiographically but the borders may be obscured Dilated pulmonary lymphatics have been demonstrated in all previous cases of CPVA They are more abundant in the connective tissue containing perilobular tissues than in the lobules The elevated pulmonary venous pressure causes this pulmonary lymphangiectasis and much edema fluid is conveyed by these channels into the systemic circulation Rywlin and Fojaco postulated that the lymphangiectasis is a retained lymphatic pattern of the fetal lung This massive dilation of pulmonary lymphatic vessels was appreciated histologically only in our Case 2 the infant with severely elevated venous pressure

Pulmonary artery pressure has been elevated to suprasystemic levels in all patients with CPVA upon whom cardiac catheterization was performed However in our case three systolic pressures in the right ventricle and aorta were equal The oxygen saturation is severely depressed and usually is similar in all heart chambers The fetal pattern of blood flow persists with right to left shunting through the foramen ovale and the ductus arteriosus Angiocardiography reveals persistent filling of pulmonary veins after the pulmonary artery injection but the left atrium and any other cardiac chamber or veins do not opacify

The anomalies of pulmonary artery atresia and TACPV occur commonly in the congenital asplenia syndrome as described by Ruttenberg and colleagues [5] Our Case 3 had both pulmonary artery and pulmonary vein atresia so that blood flowed to and from the lungs via the ductus arteriosus and intrapulmonary collateral vessels She could not have benefited from the Blalock shunt Most reported cases of CPVA have not had other anomalies and the gestational age has been 40 or more weeks

Clinical problems related to pathophysiology The tenuous existence of infants with CPVA indicates that surgical anastomosis of the verticle pulmonary vein to the left atrium should be performed immediately after diagnostic studies have been completed A surgical procedure utilizing extracorporeal circulation may allow some correction of the severe acidosis and hypoxemia Deep hypothermia and circulatory arrest may be necessary for the surgery to be accomplished Despite postmortem evidence of an adequate anastomosis for pulmonary venous flow into the left atrium no infants with this problem have survived either when the ductus arteriosus was ligated or when it was left patent [7] Factors compromising pulmonary ventilation and perfusion would be expected to persist following surgery Hypoperfusion of the lungs and severe acidosis will have suppressed formation of surfactant [7, 15] Deficiency of this antiatelectatic factor in addition to residual pulmonary congestion and lymphangiectasis will limit ventilation Hypoxemia and acidosis are stimuli for persistent

which gave rise to a large levotransposed aorta, pulmonary valve atresia, and a patent ductus arteriosus The right lung with four lobes and a trilobed left lung drained into a verticle pulmonary vein which ended blindly, it did not communicate with the let atrium or any other chamber or vessel The mid line liver was predominantly left sided The inverted gastrointestinal tract revealed the stomach on the right and the cecum and appendix on the left Stenosis of the ureters at the bladder junction had caused bilateral hydronephrosis and hydroureter

MICROSCOPIC The lungs revealed foamy macrophages and inflammatory cells, the features being those of aspiration pneumonitis The lymphatic vessels were dilated and showed no significant morphologic alteration

Comments

Developmental relationship of pulmonary and bronchial venous circulations Lucas and colleagues[1] described the common embryologic features of total anomalous connection of pulmonary veins (TACPV) and CPVA Development of the pulmonary venous system is recounted briefly The splanchnic plexus of the primordial lung buds drains into somatic veins (the cardinal system) and abdominal visceral veins (the umbilico-vitelline system) Pulmonary veins do not connect with the heart until the common pulmonary vein has formed as a diverticulum on the sinoatrial chamber of the heart As the left atrium grows it incorporates the common pulmonary vein so the individual pulmonary veins connect separately with the left atrium

TACPV or CPVA results if the common pulmonary vein either fails to develop, undergoes involution, or becomes atretic If one of these processes occurs at a time when connections of cardinal veins or umbilico-vitelline veins to the splanchnic plexus have persisted, there is TACPV If all of these primitive venous channels have already undergone the normal involution process prior to failure of the common pulmonary vein to develop and join with the pulmonary veins then the anomalous entity is CPVA Developmental failure of the common pulmonary vein from whatever cause is a pathogenetic feature of both conditions

Shaner[9] and Marchand and co workers[10] described the intimate developmental relationship of the bronchial and pulmonary circulations Bronchial veins also are formed from the splanchnic plexus and drain into cardinal veins There are two groups of bronchial veins The deep or true bronchial veins are intrapulmonary vessels related to the bronchi they drain into the pulmonary veins or the left atrium The other group is the pleurohilar veins which drain the subpleural and hilar structures of the lungs They exist when the cardinal system breaks up and drain into the azygous vein on the right and into the accessory hemiazygous or innominate vein on the left These pleurohilar veins communicate freely with the pulmonary veins and provide a decompression mechanism when pulmonary venous pressure is raised

In the first report of CPVA, Lucas and collaborators[1] described the clinical and pathological features of three infants who survived for 28, 22, and three days Their patient who died three days following surgery had a large bronchial vein originating in the right pulmonary hilus and entering the esophageal wall to connect with esophageal varices However, their other two infants and most of the other cases reported did not have such grossly dilated bronchial venous channels

Bronchial-pulmonary vascular anastomoses are known to be present in health and in congenital and acquired disease states at the arterial venous, and capillary levels[11] Von Hayek[12] estimated that under normal conditions the extensive anastomoses of bronchial and pulmonary arteries and veins are capable of conveying approximately one tenth of the postnatal pulmonary circulation This figure compares with the fraction of the right ventricular stroke volume which normally perfuses the fetal lung[13] Therefore the prenatal pulmonary circulation in CPVA may not have been compromised and there may have been little stimulus for retention of large fetal bronchopulmonary channels for collateral flow However, survival of infants with CPVA for longer than several minutes indicates that a significant amount of arterialized blood must flow to the systemic circulation

The usual stimulus for growth and proliferation of bronchial arteries and dilation of bronchopulmonary anastomotic channels in congenital heart disease is pulmonary oligemia and hypotension an effect of precapillary obstruction

Prolonged benefit of nitroglycerin ointment on exercise tolerance in patients with angina pectoris

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Sublingual nitroglycerin has long been a main stay in the symptomatic treatment of angina pectoris due to occlusive coronary disease In addition it has been shown to have salutary effects on myocardial metabolism and left ventricular function in stress states such as exer cise and pacing induced tachycardia [2] The major drawback to its use as prophylaxis for exercise induced angina is its relatively short duration of action In 1955 Davis and Wiesel demonstrated that cutaneously applied nitroglyc erin ointment could produce clinically satisfacto ry results in patients with intractable angina pectoris In the majority of patients regular use of 2 per cent nitroglycerin ointment brought about a significant decrease in the number of daily angina episodes It was not until 1974 however that a more systematic study of the duration and effect of nitroglycerin ointment upon exercise performance was undertaken

The present report will describe the effects of nitroglycerin ointment upon exercise capacity in 10 patients with chronic stable angina pectoris documented coronary disease and positive stress electrocardiography

Materials and methods

Patients The patient population consisted of nine men and one woman aged 43 to 69 years with a mean age of 53 years Criteria for admis sion to the study included

1 A history of typical stable angina pectoris for at least 1 year

2 Documentation of an unequivocally positive exercise test during at least two graded exercise stress tests—a response was considered to be positive only if it included both symptoms of angina pectoris and electrocardiographic manifes tations of myocardial ischemia (a minimum of 1 0 mm horizontal or downsloping ST segment depression at peak exercise with a resting electro cardiogram showing normal ST segments)

3 Angiographically proven coronary artery disease or a well documented myocardial infarc tion

Nine of the patients had a greater than 70 per cent reduction in the internal lumen of at least two of the major coronary arteries The remain ing patient had sustained a well documented anteroseptal myocardial infarction two years prior to this study All patients had Class II or III angina pectoris by the functional classification of the New York Heart Association All cardiac medications except for propranolol were discon tinued one week prior to the study Four patients taking propranolol were kept on an unchanging dose during the entire study None of the patients had previously received nitroglycerin ointment

The preparations studied were 2 per cent nitro glycerin ointment (Nitro Bid Marion Laborato ries) and an inert ointment as a placebo The selection of the appropriate study dosage of nitro glycerin ointment was individually determined for each patient during a two week period prior to the exercise test studies The amount of nitroglyc

From the Departm nt of Int rn l Med cine Cardiol gy Sect n Yal U iversity School of Med ine N w H en C n

Recei ed f publicatio No 15 1977
Accepted f r publi tion J 6 19 8

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constriction of small pulmonary arteries [9] Physiologic involution of the muscle coat surrounding these vessels, as in those of normal infants, can occur only gradually after hypoxemia has been alleviated

Despite these remarks of pessimism, early recognition of CPVA followed by aggressive medical and surgical treatment may result in a successful outcome Presumably the pathophysiologic changes occur only postnatally

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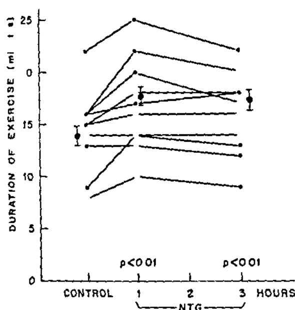


Fig 1 Changes in total duration of exercise (minutes) after administration of nitroglycerin ointment *Large solid dots* indicate mean value *solid bars* indicate standard errors

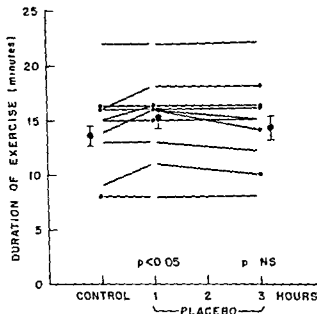


Fig 2 Changes in total duration of exercise (minutes) after administration of placebo ointment *Large solid dots* indicate mean values *solid bars* indicate standard errors

repeated at 1 and 3 hours after administration of the ointment Five patients received the active preparation first followed by the placebo the other five received the placebo first followed by the active preparation The end point of the stress test was again both angina and > 1 mm ST depression After 48 hours stress testing was repeated at 1 and 3 hours after application of the alternate preparation

Because it was recognized that the nitroglycerin ointment and placebo might be distinguishable by the patient and the physician on the basis of hemodynamics and symptomatic effects the preparations were applied by a physician other than the one administering the stress test Patients were not told that one preparation was inert but merely that the two preparations were different from each other All patients were fully informed concerning the nature and details of this study including possible unpleasant or adverse effects which they might experience Written consent was obtained for all patients after approval of the protocol by the Human Investigation Committee of Yale University School of Medicine

Data analysis Effort tolerance (ET) was calculated in the following manner work load (watts) was multiplied by the duration of exercise (minutes) for each stage of the exercise protocol

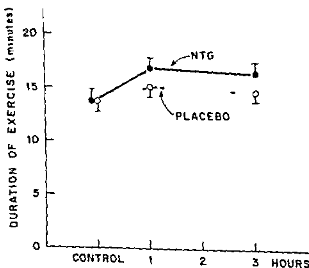


Fig 3 Changes in total duration of exercise (minutes) after administration of nitroglycerin and placebo ointments These changes are expressed as mean values ± standard errors

Effort tolerance was expressed as the sum of this product for all stages of the protocol completed by the patient Duration of exercise (DE) was expressed in minutes and represented total duration of the stress test Heart rate (HR) was calculated by computer determination and electrocardiographic print outs Blood pressure (BP) was measured using the standard cuff technique

Table I Clinical data of patient population

Patient no and initials	Age	Sex	Duration of angina	Clinical classification (NYHA)	Previous MI	Medication	ECG	Coronary arteriography	No of coronary vessels diseased
1 J A	68	M	3 yrs	II	No	None	T waves	yes	[illegible]
2 M M	51	M	2 yrs	II	No	Propranolol	T waves	yes	2
3 J M	59	M	1 5 yrs	III	No	Propranolol	WNL	yes	3
4 F R	65	M	10 yrs	II	1972	Propranolol	IWMI	yes	[illegible]
5 N A.	47	M	5 yrs	II	1974	None	IWMI	yes	3
6 L V	51	M	4 yrs	II	No	None	WNL	yes	3
7 J A	43	F	5 yrs	II	1973	None	IWMI	yes	3
8 D S	46	M	27 yrs	II	No	None	WNL	yes	3
9 H F	50	M	3 yrs	II	1974	None	ASWMI	no	[illegible]
10 J Z	48	M	4 yrs	II	No	Propranolol	T waves	yes	3

Abbreviations ASWMI = anteroseptal myocardial infarction ECG = electrocardiogram IWMI = inferior wall myocardial infarction T waves = non specific T wave changes WNL = within normal limits

Table II Summary of significance of changes (P values) during exercise at 1 hr and 3 hrs after the application of nitroglycerin versus placebo ointments

Measurements	Difference (NTG versus placebo) 1 hr	Difference (NTG versus placebo) 3 hrs
Duration of exercise	< 0.025↑*	< 0.005↑
Effort tolerance	< 0.025↑	< 0.005↑
Resting heart rate	< 0.01↑	NS†
Exercise heart rate	< 0.025↑	NS
Resting systolic blood pressure	< 0.01↓	< 0.025↓
Exercise systolic blood pressure	NS	NS
Exercise double product	NS	NS
Exercise ST segment depression	< 0.05↓	< 0.05↓

The analysis of variance between nitroglycerin and placebo treatment are provided The arrows indicate the direction of change between nitroglycerin and placebo ointments at 1 hr and 3 hrs
†Abbreviations NS = not significant

erin ointment which produced either a 10 mm Hg fall in resting blood pressure taken in the sitting position or a 10 beat per minute increase in resting heart rate or both one hour after its application was used as the patient s study dosage To accomplish dosage titration, a one half inch ribbon of nitroglycerin ointment was applied to the precordium after baselines for blood pressure and heart rate were established Blood pressure and heart rate were then checked at 10, 20, 30, 45, and 60 minutes after the application If the minimum required changes in blood pressure, heart rate, or both were not observed at one hour then the ointment remaining on the chest was thoroughly washed off This procedure was repeated the following day with one half inch ribbon increments until the study dosage for that patient was established In this study the average nitroglycerin ointment dosage was 2 4 inches (range 2 to 3 inches) The ointment was applied to an area of approximately 6 × 6 inches on the anterior chest wall and covered with plastic wrap

Protocol After admission to the study, all 10 patients underwent a control graded bicycle ergometer stress test to a level sufficient to produce both anginal pain and > 1 mm ST segment depression Exercise was performed on an upright Schwinn bicycle ergometer Each patient pedaled steadily at 50 to 60 r p m at all levels of work Exercise was begun at 25 watts (125 Kpm) and then increased by 25 watts (125 Kpm) every 4 minutes The Frank orthogonal lead system plus a CC_5 lead (bipolar chest lead right V_5 to left V) were used and monitored continuously on an Avionics Model 3000 recorder * The electrocardiogram heart rate, and blood pressure were recorded every minute throughout the exercise, at peak exercise and at 1 3, 5 and 10 minutes into the recovery period

After the control stress test, nitroglycerin ointment or a placebo was applied in a random double blinded manner and stress testing was

Avionics Irvine California

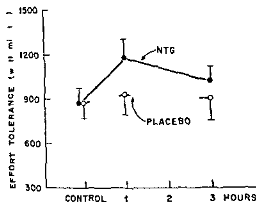


Fig 6 Changes in effort tolerance (watt minutes) after administration of nitroglycerin and placebo ointments These changes are expressed as mean values ± standard errors

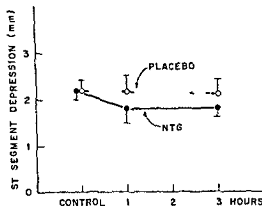


Fig 7 Changes in exercise induced ST segment depression (millimeters) after the administration of nitroglycerin and placebo ointments These changes are expressed in mean values ± standard errors

application from 877 ± 129 watt minutes in the control study to 947 ± 129 watt minutes ($p < 0.05$) However at 3 hours no significant change was observed (Fig 5) Of note only one patient of 10 exercised to a higher work load with the placebo However the total increase of effort tolerance produced by nitroglycerin ointment was significantly greater than with the placebo (Fig 6 and Table II)

Heart rate at both rest and peak exercise was unchanged from the control measurements with both preparations at 1 and 3 hours (Table III) Nitroglycerin ointment produced a consistent reduction in resting systolic blood pressure from 123 ± 6 mm Hg in the control state to 108 ± 4 mm Hg at 1 hour ($p < 0.05$) and 102 ± 5 mm Hg at 3 hours ($p < 0.005$) after its cutaneous application No changes were noted with the placebo (Table III) Systolic blood pressure at peak exercise did not differ significantly from the control stress test with either nitroglycerin or the placebo at 1 hour and 3 hours (Tables III and IV) Nitroglycerin ointment also produced a significant reduction of resting diastolic blood pressure at 1 hour and 3 hours no changes were observed after application of placebo ointment The peak exercise diastolic blood pressure did not differ in the control stress test after nitroglycerin or after the placebo (Table III) Double product at peak exercise was the same during the control stress test after nitroglycerin or after placebo ointments (Tables III and IV)

Exercise induced ST segment depression provided an objective index of myocardial ischemia Nitroglycerin ointment produced a statistically significant decrease in the magnitude of ST segment depression at peak exercise after 1 hour and 3 hours of its application The control stress test revealed 2.2 ± 0.3 mm ST segment depression which diminished to 1.8 ± 0.3 mm at 1 hour and 1.8 ± 0.29 mm at 3 hours ($p < 0.05$) with nitroglycerin ointment Placebo ointment did not produce any change in exercise induced ST segment depression (Fig 7 and Tables II and IV)

Discussion

The present study documents the ability of nitroglycerin ointment to produce an enhancement of exercise tolerance lasting up to 3 hours in patients with documented coronary artery disease and stable angina pectoris This occurs at a higher heart rate and a lower blood pressure level than with the placebo Because of the opposing direction of changes of its two components the double product was not significantly affected (Tables II and IV) The degree of myocardial ischemia estimated by the magnitude of exercise induced ST segment depression was also significantly reduced by nitroglycerin ointment for at least 3 hours (Tables II and IV)

The hemodynamic effects of nitroglycerin ointment at rest and during exercise are consistent with those reported by several earlier investigators[4] However, several aspects of this study deserve comment

It can be noted that resting heart rate 1 hour and 3 hours after application of nitroglycerin ointment did not change which differs from the findings reported in other studies[4,5] Propranolol

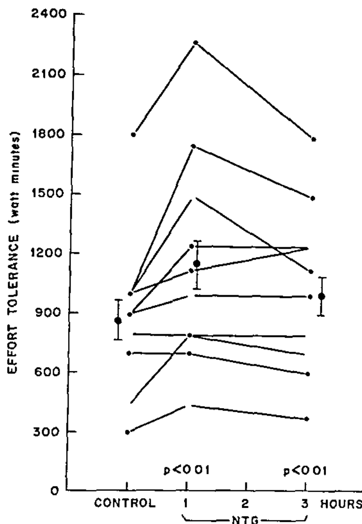


Fig 4 Changes in effort tolerance (watt minutes) after administration of nitroglycerin ointment *Large solid dots* indicate mean values *solid bars* indicate standard errors

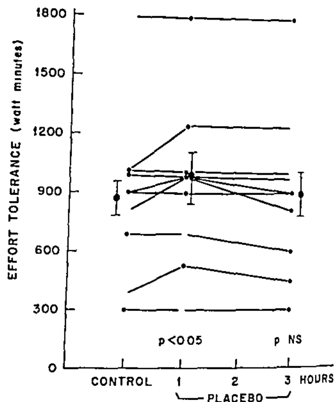


Fig 5 Changes in effort tolerance (watt minutes) after administration of placebo ointment *Large solid dots* indicate mean values *solid bars* indicate standard errors

ST segment deviation during exercise was considered abnormal if the ST segment depressed more than 1 mm in three consecutive beats measured at least 60 msec after the J point in at least one of the four leads recorded The electro cardiographic baseline from which ST segment depression was measured was the preceding PR interval All patients had a normal ST segment in the pre exercise electrocardiographic recordings

Data were analyzed using the Student s t test for paired and unpaired observations and by crossover analysis of variance between the two treatments

Results

The patient population and clinical data are summarized in Table I Nitroglycerin ointment produced a statistically significant improvement in the total duration of exercise both at 1 and 3 hours after administration Exercise duration (mean ± SE) increased from 13 7 ± 1 4 minutes in the control stress test to 16 8 ± 1 4 minutes at 1 hour after nitroglycerin (p < 0 01) and 16 3 ± 1 2 minutes at 3 hours (p < 0 01) The values for 1 and 3 hours did not differ significantly (Fig 1) The duration of exercise 1 and 3 hours after administration of placebo is shown in Fig 2 Duration of exercise did increase from a control of 13 7 ± 1 4 minutes to 15 2 ± 1 2 at 1 hours (p < 0 05), however at 3 hours there was no significant difference from the control In comparing the total duration of exercise after nitroglycerin ointment to that after the placebo (Fig 3 Table II) there was a significant increase after nitroglycerin ointment at 1 and 3 hours

In addition, eight of the 10 patients were able to exercise to a higher workload after application of nitroglycerin ointment To quantify this a score representing total effort tolerance was used in the manner described above Effort tolerance increased significantly in response to nitroglycerin ointment from 877 ± 129 watt minutes in the control period to 1165 ± 173 watt minutes at 1 hour (p < 0 01) Effort tolerance was still significantly higher than control at 3 hours after nitroglycerin application 1040 ± 137 (p < 0 01) (Fig 4) The placebo produced a statistically significant increase in effort tolerance 1 hour after

in this study were typical angina pectoris and > 1 mm ST segment depression on the electrocardiogram The peak exercise double product an index of myocardial oxygen demand remained unchanged at 1 hour and 3 hours after application of nitroglycerin ointment when it was compared to the control or to the placebo values It must be noted however that patients performed higher levels of external work measured as duration of exercise and exercise tolerance (Tables II and IV) before they reached the established end points of our protocol This dissociation between internal (oxygen demand) and external work (exercise tolerance) is due in part to the sustained hemodynamic effects of nitroglycerin upon peripheral circulation (Table III)

Over all myocardial ischemia was evaluated in our study by the magnitude of exercise induced ST segment depression When compared to the control stress tests or to the placebo stress tests exercise ST segment depression was significantly reduced 1 hour and 3 hours after nitroglycerin administration If the index of myocardial oxygen demand in our study was unchanged and the magnitude of myocardial ischemia was reduced we postulate that there was either an improvement in oxygen supply to the myocardium or a reduction in oxygen consumption This is not apparent in the double product and therefore does not explain our clinical findings It is well recognized that a major action of nitroglycerin is predominantly to decrease oxygen demands through its peripheral effect on venous capacitance and arteriolar resistance[7] It is still controversial whether significant coronary vasodilatation occurs in patients with coronary artery disease and angina pectoris following the administration of nitroglycerin Although it has been stated that nitrates cause coronary vasodilatation [6] intracoronary arterial administration of nitroglycerin fails to alleviate angina induced by atrial pacing while sublingual nitroglycerin relieves angina presumably by its peripheral effects[12] Studies on total[13] regional [5 7] and subendocardial [7 8] coronary blood flow have yielded contradictory results Some authors[7] state that nitroglycerin while leaving total myocardial blood flow unchanged increases subendocardial blood flow in normal and ischemic regions of the ventricle thus minimizing the severity of myocardial ischemia The reduction in exercise induced ST segment depression observed in our patients after the application of nitroglycerin ointment could represent this phenomenon However the alternative explanation is that a major reduction in oxygen consumption has occurred in our patients after the administration of nitroglycerin ointment which is not reflected in the double product Several studies have demonstrated a significant reduction of left ventricular filling and the consequent reduction in wall tension after the administration of nitroglycerin

Clinical use of nitroglycerin ointment There is no accepted value for maximal efficacy or maximal duration of action for a nitrate Although the degree and duration of improvement in exercise tolerance after the administration of nitrates may increase when larger doses of the drugs are administered there are clear physiologic limits of nitrate dosage that should not be exceeded because of potentially adverse effects For these reasons we examined the effects of a dose of nitroglycerin effectiveness by purely arbitrary criteria For each individual patient the amount of nitroglycerin ointment which produced a 10 mm Hg fall in resting systolic blood pressure or a 10 beat per minute rise in resting heart rate or both one hour after the application of the active preparation was used as the test dosage It was difficult to predict how much ointment would produce the desired hemodynamic effects Our average dose was 2 4 inches (range 2 to 3 inches) The protocol for dose titration avoided potential side effects of nitroglycerin overdose and our patients did not experience dizziness or orthostatic symptoms Nitroglycerin ointment was applied over a substantial area of skin on the chest wall (6 × 6 inches) Because there is some evidence that a given dose applied over a smaller surface area may result in smaller and less predictable hemodynamic changes the total surface area of 36 square inches was used Data concerning the time course of transcutaneous nitroglycerin absorption are lacking presumably the duration of improvement in exercise tolerance produced by nitroglycerin ointment reflects the rate of entry of the drug into the circulation

Clinical implications Topical application of nitroglycerin as an ointment has been known for a long time but only recently has there been much interest in its use Hemodynamic effects persisting for 3 to 6 hours have been reported [6 20] This and two previous studies[4 5] convincingly demonstrate improved exercise tolerance from 1

Table III Summary of hemodynamic effects of exercise before and after nitroglycerin and placebo ointments (mean ± Standard Error)

	HR	*SBP*	*DBP*	*DP (HR × SBP)*
Control				
Resting	77 5 ± 4 3	123 ± 6	78 ± 3	967 8 ± 9/ 3
Peak exercise	123 4 ± 6 5	162 ± 13	69 ± 6	?048 7 ± ?85 9
3 min post exercise	83 8 ± 3 5	117 ± 4	76 ± 2	9/5 9 ± 58 8
NTG 1 hr				
Resting	74 7 ± 3 6	108 ± 4	67 ± 3	809 9 ± 57 3
Peak exercise	134 0 ± 7 0	152 ± 7	71 ± 4	2074 6 ± 187.5
3 min post exercise	90 8 ± 4 5	100 ± 5	66 ± 4	901 3 ± 53 6
NTG 3 hrs				
Resting	80 7 ± 4 2	102 ± 5	69 ± 3	831 5 ± 7 0
Peak exercise	132 1 ± 7 4	152 ± 9	65 ± 3	2050 0 ± 208 3
3 min post exercise	91 1 ± 5 6	105 ± 6	65 ± 4	973 7 ± 88 5
Placebo 1 hr				
Resting	69 3 ± 3 4	114 ± 5	74 ± 3	804 6 ± 69 7
Peak exercise	121 8 ± 7 7	153 ± 13	70 ± 4	1935 9 ± 300 6
3 min post exercise	83 6 ± 5 4	113 ± 6	72 ± 3	948 9 ± 81 4
Placebo 3 hrs				
Resting	75 2 ± 4 2	113 ± 6	72 ± 3	867 8 ± 88 5
Peak exercise	126 6 ± 7 3	155 ± 12	71 ± 3	2005 7 ± ?7 5
3 min post exercise	85 3 ± 4 6	115 ± 6	71 ± 3	987 8 ± 85 9

Abbreviations DBP = diastolic blood pressure (mm Hg) DP = double product (mm Hg × min) HR = heart rate (beat per minute) NTG = nitroglycerin ointment SBP = systolic blood pressure (mm Hg)

Table IV Summary of significance of changes (P values) at rest and during exercise between the control state and after nitroglycerin and placebo ointment

Measurements	*NTG*†		*Placebo*	
	1 hr	*3 hrs*	*1 hr*	*3 hrs*
Duration of exercise	< 0 01↑	< 0 01↑	< 0 05↑	NS
Tolerance	< 0 01↑	< 0 01↑	< 0 05↑	NS
Resting heart rate	NS	NS	NS	NS
Exercise heart rate	NS	NS	NS	NS
Resting systolic blood pressure	< 0 05↓	< 0 05↓	NS	NS
Exercise systolic blood pressure	NS	NS	NS	NS
Exercise double product	NS	NS	NS	NS
Exercise ST segment depression	< 0 05↓	< 0 05↓	NS	NS

Significant changes from control studies by the Student t test are identified by the appropriate p value The arrows indicate the direction of change
†Abbreviations NTG = nitroglycerin NS = not significant

was not discontinued in four patients who were receiving it prior to the study (Patients No 2 3 4 and 10) Their doses were maintained unchanged throughout the entire investigational period It is very probable that the beta adrenergic blockade achieved in our patients prevented the expected increase in heart rate It is unclear why our patients were able to exercise longer and at a higher work load 1 hour after the application of the inert ointment (Fig 2 and Table IV) It is possible that during the study a conditioning effect occurred but it is unlikely that this factor played an important role, because all patients had only two previous exercise tests which were terminated by the appearance of angina and ST segment depression prior to entering the study Furthermore these exercise tests were terminated at the same work load and double product In addition the application of nitroglycerin ointment was done in a randomized manner which would minimize any significant effect produced by early exercise conditioning Perhaps the most plausible explanation for this phenomenon was a placebo effect due to patient belief that an active medication rather than an inert ointment was being used In any case the increase was significantly less than that seen with nitroglycerin ointment (Table II)

Mechanism of beneficial effects of nitroglycerin ointment Analysis of the hemodynamic and electrocardiographic changes before and during exercise suggests that nitroglycerin ointment may produce its effects through changes both in myocardial oxygen demand and in myocardial oxygen supply The exercise stress test end points

in this study were typical angina pectoris and > 1 mm ST segment depression on the electrocardiogram The peak exercise double product, an index of myocardial oxygen demand remained unchanged at 1 hour and 3 hours after application of nitroglycerin ointment when it was compared to the control or to the placebo values It must be noted however that patients performed higher levels of external work measured as duration of exercise and exercise tolerance (Tables II and IV) before they reached the established end points of our protocol This dissociation between internal (oxygen demand) and external work (exercise tolerance) is due in part to the sustained hemodynamic effects of nitroglycerin upon peripheral circulation (Table III)

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Clinical implications Topical application of nitroglycerin as an ointment has been known for a long time but only recently has there been much interest in its use Hemodynamic effects persisting for 3 to 6 hours have been reported[4,6,20] This and two previous studies[5] convincingly demonstrate improved exercise tolerance from 1

to 3 hours after its administration Thus, nitroglycerin ointment is one of the nitrate preparations proven to have long lasting effects on angina pectoris[21] Clinical settings where it may be of value could include patients with nocturnal angina pectoris, as prophylactic nitrate preparation in patients with chronic exertional angina pectoris, or in patients with unstable angina pectoris It must be realized, however, that the cutaneous form of nitroglycerin is a potent and long acting agent, and there is always danger of delivering a large amount of active nitrate to the circulation over a relatively short period of time thereby producing significant symptoms of overdosage

Summary

The effect on exercise tolerance of 2 per cent nitroglycerin ointment and placebo was studied on the bicycle ergometer in 10 patients with angina pectoris, a positive exercise test, and documented coronary artery disease After a control stress test sufficient to produce angina pectoris and > 1 mm horizontal or downsloping ST segment depression, nitroglycerin ointment or placebo was administered in a random double blinded manner and stress tests were repeated at 1 hour and 3 hours End points for the exercise stress test were angina and 1 mm ST segment depression Forty eight hours later, stress tests were again performed at 1 hour and 3 hours after administration of the alternate preparation Work load (watts) plus duration of exercise (minutes) were calculated for each stage of the bicycle ergometer protocol and exercise tolerance was expressed as the sum of this product for all stages completed

Nitroglycerin ointment produced a significant increase in exercise tolerance from a control value of 877 ± 129 watt minutes to 1165 ± 173 watt minutes at 1 hour and 1040 ± 137 watt minutes at 3 hours Duration of exercise also increased significantly after nitroglycerin ointment from 13 7 ± 1 4 minutes in the control stress test to 16 8 ± 1 4 minutes at 1 hour and 16 3 ± 1 2 minutes at 3 hours Exercise induced ST segment depression decreased significantly at 1 hour and 3 hours after nitroglycerin ointment but not after the placebo

The placebo produced a small, but statistically significant, increase in exercise tolerance and duration of exercise at 1 hour after its application However, these increases were significantly smaller than the one observed after nitroglycerin ointment No changes were observed 3 hours after application of the placebo Double product at peak exercise was unchanged after nitroglycerin or placebo ointments at 1 hour and 3 hours

These data indicate that nitroglycerin ointment is capable of producing an improvement in exercise tolerance and a reduction in the magnitude of exercise induced ST segment depression up to 3 hours in patients with coronary artery disease and angina pectoris

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An evaluation of the results of left ventricular aneurysmectomy Use of a simplified method for analysis of the left ventriculogram

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Resection of left ventricular aneurysms frequently relieves angina pectoris, systemic embolization, intractable congestive heart failure and arrhythmias [1-6] In order to improve the operative results, attempts have been made to develop preoperative angiographic criteria which will permit better patient selection This development is dependent on two factors—an improved understanding of the disordered circulatory physiology in patients with ventricular aneurysm, and some objective description of the surgical results The latter is necessary to determine the validity of any developed preoperative criteria

Present understanding of cardiac dysfunction due to left ventricular aneurysm depends largely on analyses of the right anterior oblique ventriculogram This two dimensional figure has usually been divided into aneurysmal and contractile portions, and measurements from each converted mathematically to volumes of a variety of solid geometrical figures [7-11] Such conversions assume that the ventriculographic segments approximate the shape of a selected three dimensional figure whose volume is calculable These assumptions have not been tested experimentally, and if inaccurate, would provide erroneous calculated volumes and functional data, less useful than the two dimensional measurements themselves Methods have also been described using ventriculographic perimeters and their aneurysmal and contractile sub segments which avoid the need for assumptions of this type [1, 13]

The results of surgery have been described almost entirely in clinical terms Most series include a large proportion of patients who have also had coronary artery bypass grafts The uncertain effects of these grafts on ventricular function invalidate the use of such cases in the study of aneurysmectomy results

The present study attempts to avoid these difficulties by presenting a series of 23 consecutive patients who have undergone left ventricular antero apical aneurysmectomy alone Patients treated with valve replacement or coronary artery bypass grafting were specifically excluded Seventeen of the 19 surgical survivors underwent follow up cardiac catheterization A simple method for the two dimensional analysis of both pre and postoperative left ventricular angiograms is described which avoids the assumption that any

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Received for publication Nov 19 1977
Accepted for publication Jan 10 1978

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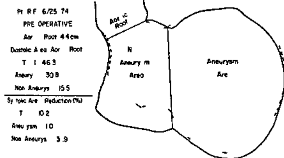


Fig 1 Example of right anterior oblique ventriculographic outline with division into aneurysmal and nonaneurysmal segments. Preoperative

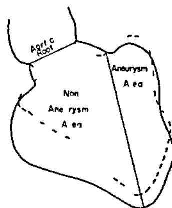


Fig 2 Example of right anterior oblique ventriculographic outline with division into aneurysmal and nonaneurysmal segments Postoperative

ventricular segment approximates the shape of a known geometric figure By these means it was found that errors in preoperative case selection accounted for only some of the postoperative failures The remainder were explained by intra operative and postoperative developments which could not have been predicted preoperatively

Materials and methods

Patients Between May 1970 and March 1976 57 left ventricular aneurysms were resected in this institution In 23 of these cases the aneurys mectomy was the only surgical procedure there being no associated coronary artery bypass grafts or valve replacements These 23 cases form the basis of this report There were 18 males and five females whose ages ranged between 29 and 71 years at the time of surgery All patients had had previous anterior wall myocardial infarctions with residual typical electrocardiographic Q waves in the precordial leads

Every patient had a preoperative cardiac catherization with left ventriculography in the right anterior oblique projection which demon strated an aneurysm of the anterior and apical walls The diagnosis of left ventricular aneurysm depended on the demonstration of akinetic or dyskinetic wall segments but in a few instances severely hypokinetic segments were also present Coronary arteriograms were carried out in every instance using multiple views in both right and left anterior oblique projections and all 23 patients had severe occlusive disease of the left anterior descending coronary artery In 19 cases this vessel was completely occluded and in four the occlusion was judged to be 75 per cent or greater In 17 of the 23 patients coronary artery disease (50 per cent occlusion or greater) was present in vessels other than the left anterior descending coronary artery Bypass grafts were not utilized in these patients for a variety of reasons such as insufficiently severe proximal stenosis or because of small distal arterial cali ber

The indications for aneurysmectomy were often multiple in the same patient and included peripheral embolization (3) incapacitating con gestive heart failure (21) angina pectoris (8) and ventricular arrhythmias (3)

Left ventricular aneurysmectomy was carried out without coronary artery bypass or other surgical procedures from one month to three years following the myocardial infarction The procedure was performed under cardiopulmonary bypass utilizing modified hypothermia at 32° C in all cases The aneurysm was totally excised with the exception of a narrow fibrous rim at its base for suture placement

There were four in hospital deaths and 19 long term survivors Seven of the survivors underwent repeat follow up cardiac catheterization on request of their referring physician because of persistent or recurrent symptoms All of the others were invited to be restudied with the approval of their referring physician for a more precise determination of their postoperative status Two patients who were symptomatically improved refused restudy and there were there fore 17 follow up catheterizations These repeat cardiac catheterizations were performed between 5 and 44 months postoperatively with an average of 25 3 months

An evaluation of the results of left ventricular aneurysmectomy Use of a simplified method for analysis of the left ventriculogram

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Resection of left ventricular aneurysms frequently relieves angina pectoris, systemic embolization, intractable congestive heart failure, and arrhythmias [1-6] In order to improve the operative results, attempts have been made to develop preoperative angiographic criteria which will permit better patient selection This development is dependent on two factors—an improved understanding of the disordered circulatory physiology in patients with ventricular aneurysm, and some objective description of the surgical results The latter is necessary to determine the validity of any developed preoperative criteria

Present understanding of cardiac dysfunction due to left ventricular aneurysm depends largely on analyses of the right anterior oblique ventriculogram This two dimensional figure has usually been divided into aneurysmal and contractile portions, and measurements from each converted mathematically to volumes of a variety of solid geometrical figures [7-11] Such conversions assume that the ventriculographic segments approximate the shape of a selected three dimensional figure whose volume is calculable These assumptions have not been tested experimentally, and if inaccurate, would provide erroneous calculated volumes and functional data less useful than the two dimensional measurements themselves Methods have also been described using ventriculographic perimeters and their aneurysmal and contractile sub segments which avoid the need for assumptions of this type [1, 13]

The results of surgery have been described almost entirely in clinical terms Most series include a large proportion of patients who have also had coronary artery bypass grafts The uncertain effects of these grafts on ventricular function invalidate the use of such cases in the study of aneurysmectomy results

The present study attempts to avoid these difficulties by presenting a series of 23 consecutive patients who have undergone left ventricular antero apical aneurysmectomy alone Patients treated with valve replacement or coronary artery bypass grafting were specifically excluded Seventeen of the 19 surgical survivors underwent follow up cardiac catheterization A simple method for the two dimensional analysis of both pre and postoperative left ventricular angiograms is described which avoids the assumption that any

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The outline of the ventriculogram images were traced at end systole and at end diastole from sinus beats at least two cycles following the nearest preceding premature ventricular beat Systolic and diastolic images were not aligned along a common mid aortic root to apex axis, since in the presence of antero apical aneurysm no distinct apical point could be constantly found. Furthermore there is no evidence that the nonaneurysmal left ventricular segment con tracts uniformly about such an axis The figures were aligned however by superimposing the systolic and diastolic aortic root shadows and irregular portions of the left ventricular perimeter common to both systole and diastole

In most instances it was possible to find a point on the inferior and anterior ventricular perimeter which clearly demarcated the contractile from the noncontractile segments These two points were connected by a straight line in systole and diastole thus separating the aneurysmal from nonaneurysmal left ventricular areas (Figs 1 and 2) In a few instances the contractile and aneu rysmal perimeters were connected by a relatively long hypokinetic segment In these cases the mid point of this hypokinetic junction was chosen as the separation point between aneurysm and nonaneurysm sections

The aneurysmal and nonaneurysmal areas thus defined were measured in both systole and diastole by planimetry and their respective perim eters were delineated using a map measurer Aneurysm size is also presented as a percentage of the total ventricular area The percentage reduc tion in total area aneurysmal area nonaneurys mal area and their respective perimeters during systole was also calculated This calculation is analogous to that of the ejection fraction when ventricular volumes are used

In order to compare pre and postoperative areas in these noncalibrated ventriculograms the aortic root diameter was considered a reference dimension and assumed not to change significant ly between the two studies All measured areas were converted to ratios using the aortic root

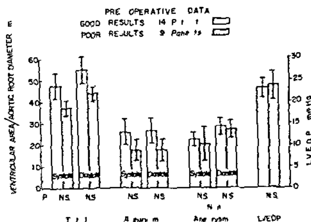


Fig 5 Comparison of preoperative right anterior oblique ventriculographic areas corrected for aortic root diameter and left ventricular end-diastolic pressures in Group 1 and Group 2.

Table I Results of ventricular aneurysmectomy Group 2—mean values

Measurement	*Preoperative*	*Postoperative*
Ventricular area/aortic root diameter (diastole) (cm)		
Total	39 2	42.3
Aneury m	11 1	19.5
Non Aneurysm	28 1	22.8
% Systolic area reduction		
Total	19.5	5 4
Aneurysm	3.5	2.9
Non Aneurysm	22 7	6 2

diameter as the denominator and the pre and postoperative ratios were compared

Statistical analyses were carried out using Student s t test for paired and unpaired data

Results

Clinical results of aneurysmectomy The patients were divided as described above into two groups Group 1 included 14 patients who were improved by clinical and catheterization criteria only Eleven patients in this group were greatly improved and included five who had returned to work two who were asymptomatic and four others who had only mild residual angina Two patients of the remaining three had persistent bothersome angina but were included in Group 1 because the congestive heart failure for which they underwent surgery had improved both symptomatically and hemodynamically

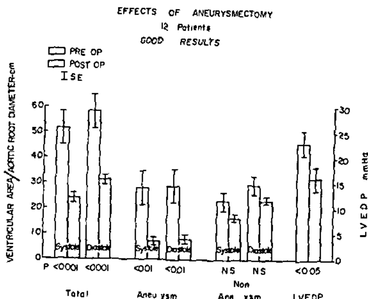


Fig 3 Effects of left ventricular aneurysm resection on right anterior oblique ventriculographic areas corrected for aortic root diameter and on left ventricular end diastolic pressures

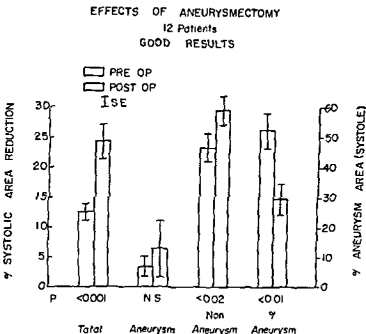


Fig 4 Effects of left ventricular aneurysm resection on the per cent reduction during systole of the right anterior oblique ventriculographic areas and on the percentage of the total area which is aneurysmal

At the time of hospitalization for restudy each patient underwent a complete history physical examination and routine laboratory work which included a chest x ray and ECG The two patients who refused recatheterization were interviewed by telephone and their referring physicians records were reviewed

The 23 patients were divided into those who improved postoperatively (Group 1—14 patients) and those who did not (Group 2—nine patients)

In assigning patients to these groups, emphasis was placed on their history, especially relief of preoperative presenting complaints, return to work levels of activity achieved, and satisfaction with the quality of life The laboratory evaluation used for confirmation of patient referral to the groups included heart size by chest x ray, changes in left ventricular end diastolic pressure and pulmonary artery pressure, but did not include variations in left ventriculographic parameters described below The addition of laboratory data to symptomatic evaluation was especially valuable in four patients Two had persistent but not disabling angina postoperatively yet were improved of their preoperative heart failure and a third had multiple symptoms probably noncardiac in origin These three showed striking improvement in heart size and catheterization findings and were therefore assigned to Group 1 One other patient was symptomatically better but had changed to a life style requiring minimal exertion Laboratory data in this patient showed no improvement in pulmonary artery pressure, slight increase in left ventricular end diastolic pressure and no improvement in heart size She was assigned to Group 2

Group 1, those 14 patients who by symptoms and laboratory evaluation had a good response to surgery were followed for a mean of 25 6 months (range 9 to 44 months) Group 2, those nine patients who had a poor response to surgery, included the four postoperative deaths and the five other patients followed for an average of 21.2 months (range 5 to 34 months)

Catheterization technic Pre and postoperative catheterizations were carried out by the retrograde arterial technic using either the brachial or femoral approach Intracardiac pressures were sensed by strain gauges whose outputs were amplified and then recorded on a strip chart recorder All pressures were referred to mid chest as a zero level Left ventriculograms were analyzed only in the right anterior oblique (30 degrees) projection although many had left anterior oblique views as well The right heart and pulmonary artery were catheterized in the usual fashion and cardiac output was measured using the standard Fick or indocyanin green indicator dilution technic

Analysis of the right anterior oblique left ventriculogram The method to be described for

the analysis of pre and postoperative left ventric ulograms was chosen so that angiograms from any institution could be used in this study There was no constant tube to target distance no calibration grid and therefore no calculable ventricular volumes

The outline of the ventriculogram images were traced at end systole and at end diastole from sinus beats at least two cycles following the nearest preceding premature ventricular beat Systolic and diastolic images were not aligned along a common mid aortic root to apex axis since in the presence of antero apical aneurysm no distinct apical point could be constantly found Furthermore there is no evidence that the nonaneurysmal left ventricular segment con tracts uniformly about such an axis The figures were aligned however by superimposing the systolic and diastolic aortic root shadows and irregular portions of the left ventricular perimeter common to both systole and diastole

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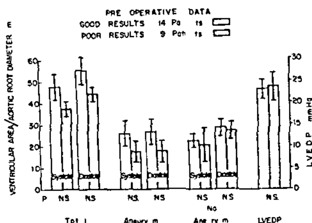


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% Systolic area reduction		
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Non Aneurysm	2? 7	6.2

Statistical analyses were carried out using Student s t test for paired and unpaired data

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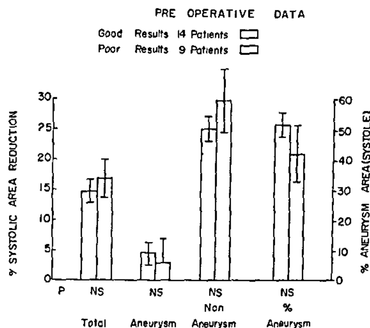


Fig 6 Comparison of preoperative per cent reduction during systole of the right anterior oblique ventriculographic areas and the per cent of the total area which is aneurysmal in Group 1 and Group 2

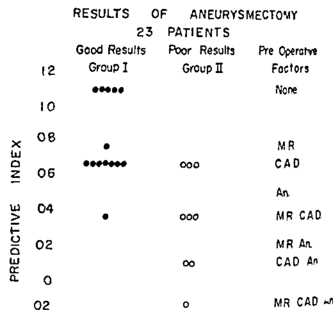


Fig 7 Distribution of predictive indexes of surgical success calculated from a multiple regression equation using mitral regurgitation *(MR)* coronary artery disease outside the aneurysm distribution *(CAD)* and excessively large or small aneurysm size *(An)* as independent variables

The remaining patient had persistent symptoms but the chest x ray and catheterization findings were improved

The nine patients in Group 2 responded poorly to surgery Four of these nine patients died in the immediate postoperative period and all four showed evidence of low cardiac output after surgery The immediate causes of death in these cases included complications of the intra aortic balloon assist device in one patient, postoperative infections in two (lung abscess and sepsis), and intractable ventricular tachycardia and fibrillation in the last Five surgical survivors in this group had recurrent symptoms of congestive heart failure In addition, one patient sustained a recurrent myocardial infarction and another had ventricular ectopic arrhythmias which were difficult to control

Angiographic results of aneurysmectomy

Group I Fourteen patients 12 follow up cardiac catheterizations Fig 3 shows the results of aneurysmectomy on the planimeterized ventricular areas corrected for aortic root diameter There were significant systolic and diastolic reductions in the total and aneurysmal areas whereas the nonaneurysmal areas were not significantly changed These findings would be expected since the only surgical attack was on the aneurysm itself

The effect of surgery on the per cent systolic area reduction in the three ventricular segments is displayed in Fig 4 This value was significantly improved for the entire heart (+12 per cent) and for the nonaneurysmal segment (+6 per cent) but not in the aneurysm itself Also shown in this figure is the significant postoperative reduction in percentage of the total systolic ventricular area occupied by the aneurysm

Preoperatively, only five patients had aneurysmal areas which were larger in systole than diastole Of these five the largest bulge was 5 per cent and the remaining four increased in area only by 1 per cent Bulging of the aneurysm was therefore an uncommon finding in this series and the phenomenon was not significantly altered by aneurysmectomy

Group II Nine patients five follow up catheterizations The number of follow up studies is small and the value of statistical analysis uncertain, but it is apparent from Table I that there was no change as a result of aneurysmectomy of the average total ventricular area, the aneurysmal or nonaneurysmal areas all corrected for aortic root diameter In contrast with the data in Group 1 there was a marked decrease in the per cent systolic area reduction of both contractile and total ventricular area following surgery

Comparison of Group I and Group II preoperative ventriculograms Figs 5 and 6 show that

Table II Results of ventricular aneurysmectomy Group II—9 patients

Patients	Pre Op factors				Peri Op factors		Post Op factors
					M R		
	CAD other than LAD	Small an† area < 25%	Large an area > 87%	M R 1 2+	1 2+	3-4+	Worse CAD (not LAD)
J C	X	X					
R. K	X						
A. C	X			X			
M. S	X						
E. M	X	X		X		Y	X
E. Sm	X			X			X
F M.	X					X	
C H.	X		X				
E. So	X			X		X	
Group 1 Good Results 14 patients	8	0	0	2 both relieved post op	5	0	0 (2 in LAD)

Post operative d ath.
†Abbre iat ns An = aneurysm CAD = coron ry artery disease (50% stenosis or great) LAD = left terior descending coronary artery MR = mitral regurgitati n

none of the angiographic area measurements made preoperatively effectively separated those patients who did well from those who did poorly following surgery

Perimetry The entire analysis was carried out using perimeters of the ventriculographic images rather than areas In general the results were not as clear as those using planimeterized areas There was a significant decrease in the perimeter of the aneurysmal segments (corrected for aortic root diameter) and in the per cent of the perimeter which was aneurysmal before and after surgery in Group 1 patients Perimeter measurements as with area measurements provided no preoperative separation between the two groups Systolic perimeter shortening of the contractile segment was less than expected because of invagination and folding of the ventricular margins This limited the usefulness of perimeter measurements in the calculation of per cent systolic perimeter reduction

Hemodynamics The reduced left ventricular end-diastolic pressure after surgery in Group 1 patients (Fig 3) was expected because elevation of this value was one basis for referral of patients to each of the two groups But the preoperative values alone did not separate Group 1 from Group 2 patients (Fig 5)

Measurements of cardiac output by either the Fick or indicator dilution methods were carried out in 10 preoperative and 13 postoperative studies Although these data were not consistently available review of the results showed them to be of little use in predicting postoperative results

Separate analysis of Group II patients As a group there were no preoperative hemodynamic or angiographic features which completely separated the patients who did poorly from those who did well Review of each case separately however identified individual factors which could be used to improve selection of cases for surgery This analysis is displayed in Table II and can be divided into pre intra and postoperative factors

Two patients had preoperative angiograms which demonstrated the smallest aneurysms in the entire series (9 and 13 per cent) These two patients had surgery in 1971 and were among the earliest patients to undergo aneurysmectomy in this institution It appears that the heart failure present in these patients was as much related to widespread coronary artery disease and/or mitral insufficiency as it was to the aneurysms Their resection therefore offered less hope of improvement than in other patients The patient whose aneurysm was next in percentage of total ventricular area (25 per cent) did well postoperatively Another patient preoperatively had the largest per cent aneurysm (96 per cent) and the smallest non aneurysmal segment area of the series In this instance there was insufficient remaining contractile myocardium to support the circula

tion following surgery The patient whose aneurysm was second largest (87 *per cent*) had, in contrast, striking benefit from surgery Four of the nine patients in Group 2 showed mild degrees of mitral regurgitation on their preoperative angiogram, while only two of 14 patients in Group 1 had this lesion All nine patients *in Group 2 had* significant narrowing of coronary arteries supplying non aneurysmal myocardium, but eight of 14 in Group 1 also displayed this finding

The three preoperative factors most influential *in predicting surgical* results were coronary artery disease outside the aneurysm distribution, mitral regurgitation and excessively small or large aneurysms Each patient was assigned a value of either 1 0 *or zero for* each factor, depending upon its presence or *absence, respectively Patients* in Group 1 *were designated as 1 0 and those* in Group 2 were given zero Using surgical outcome as the dependent variable and the three preoperative factors as independent variables, a multiple regression analysis was carried out using a standard computer program The multiple correlation coefficient obtained was 0 67 ($F = 5\ 05$, $p < 0\ 01$), indicating a significant influence of these preoperative *factors on the surgical results* Using the multiple regression equation a value for the dependent variable was calculated for each patient, and these values (predictive index) are shown in Fig 7 The overlap between Groups 1 and 2 obviates the use of the index to predict surgical results with accuracy But the display does suggest the effects of the preoperative factors, alone or in combination on the risks of a poor surgical result For example among those patients with coronary artery disease outside the aneurysm seven of 10 patients did well, but when mitral insufficiency was added only one of four had a good result

Severe mitral regurgitation probably induced at surgery contributed to the poor results in three instances In two of these milder mitral insufficiency was present preoperatively Aneurysmectomy also relieved mild mitral regurgitation in one patient in Group 2 and two patients in Group 1

Several of the poor surgical results could be explained by postoperative findings also not predictable from preoperative studies Two patients developed advancing coronary artery disease in vessels supplying the remaining contractile myocardium In Group 1 there were also two patients with advancing coronary artery disease located in the anterior descending coronary artery, a vessel supplying previously infarcted myocardium

Discussion

The purpose of the present study was to evaluate the results of left ventricular aneurysmectomy *To aid in the evaluation* a simple angiographic method was utilized with the hope that it would improve the selection of patients for surgery In order to determine the usefulness of any preoperative angiographic method, postoperative evaluation should include cardiac catheterization of good and poor results in addition to a symptomatic review Furthermore, the surgical series must be uncontaminated by patients treated with procedures other than aneurysmectomy, such as coronary artery bypass grafts or valve replacement Although postoperative recatheterization has been previously reported[4, 14-16] these series did not exclude patients with concomitant coronary artery surgery, did not include a significant proportion of survivors, or did not analyze the ventriculograms in detail

The circulatory disability induced by left ventricular aneurysm secondary to coronary artery atherosclerosis, has a dual nature The loss of contractile myocardium in the aneurysm, its size and whether or not it absorbs cardiac energy by bulging during systole represents one liability The contractility of the remaining segment and the adequacy of its blood supply is the second Both aspects of this disorder are amenable to study using the left ventricular angiogram and coronary arteriography Many previous efforts have converted single plane two dimensional angiographic images of the aneurysmal and contractile ventricular areas to volumes using formulas for a variety of known geometrical shapes Precedent for this approach has arisen from the established usefulness of volumes calculated from the normal ventricle using the prolate ellipsoid as a three dimensional shape approximation[17, 18] The validity of this technique in the non aneurysmal ventricle has solid experimental support, but no such support has been described for any of the shapes chosen to represent the aneurysmal ventricle or its subdivisions *It therefore* seems doubtful that the conversion of two dimensional measurements to volumes will improve the utility of the original right anterior

oblique angiographic figure Yet several recent studies using clinical status only as an end point have suggested angiographic methods for the prediction of surgical results Watson and colleagues found a rough relationship between postoperative clinical class and ejection fraction of the contractile segment assumed to be a hemispheroid Lee and associates [9] calculated the difference between the ejection fraction taken from the angiographic figure (assuming an ellip soidal shape) and the ejection fraction of a theo retical spherical model the akinetic fraction of which was determined by perimetry This differ ence between ejection fractions was useful in predicting operative survival but did not relate to long term or over all survival In future inclusion of measurements taken from the left anterior oblique angiographic figure might allow better three dimensional assessment of the antero apical aneurysmal volume

Absolute volume measurements necessitate that angiographic magnification factors be con trolled To insure that such calculated volumes applied to all patients referred to a medical center for left ventricular aneurysmectomy patients studied in outlying institutions would need repeat preoperative catheterization The ejection frac tions described above and the present method are volume independent require no special equip ment and are applicable to satisfactory left ventriculograms obtained in any institution These ventriculographic measurements appear of some use since they demonstrate the changes expected from the division of cases into good and poor surgical results The value of these methods are limited however in predicting results Our technic would improve case selection by rejecting patients with the largest or smallest aneurysms but by no other measurement The other more complex ventriculographic technics have been little more effective in this regard and have not been subjected to a similar analysis using postop erative catheterization study It also seems possi ble that no area or volume method will be of great predictive value since surgical failures in large measure depended on factors apart from the ventriculogram

Analysis of these factors showed them to be of heterogeneous origin divisible into pre intra and postoperative types The non ventriculo graphic preoperative factors more frequent among surgical failures included the presence of coronary disease in arteries supplying the contractile myocardium and mitral insufficiency The former has been previously described as a negative factor in predicting surgical success [19] Preoperative mitral insufficiency has not been emphasized previously but should be a warning to the surgeon since some patients with this finding were relieved of mitral insufficiency by surgery but others made worse The postoperative factor contributing to unsatisfactory surgical results was advancing coronary artery disease in vessels supplying the contractile ventricular segment a development which is unpredictable from the preoperative evaluation

Aneurysmal bulging has been indicted in the past as a cardiac liability in addition to aneurysm size [21] especially in those patients whose aneu rysm develops within a few weeks of acute myocardial infarction Review of our angiograph ic data however failed to reveal impressive aneu rysmal bulging in any of the preoperative angio grams including those in patients whose aneu rysms developed within weeks of myocardial infarction The present angiographic methods however should be useful in this regard in future patients where aneurysmal bulging may be important

This study indicates that ventricular aneurys mectomy in many patients is a valuable proce dure as presently carried out that the preopera tive ventricular and coronary angiogram can be used to better select patients for the procedure but that some unsatisfactory results are inevita ble from advancing coronary artery disease It also raises questions but no answers for the cardiac surgeon in determining how much aneu rysm to resect how small or large to leave the ventricular cavity for provision of an optimum volume to prevent postoperative mitral regurgita tion Only routine postoperative recatheteriza tion will permit the surgeon to relate operating room experience to surgical results

Summary

Twenty three patients underwent left ventric ular aneurysmectomy without coronary artery bypass or other surgical procedure Fourteen patients (Group 1) benefitted from surgery and nine fared poorly (Group 2) including the four postoperative deaths Among the 19 survivors 17 had postoperative catheterizations Pre and postoperative left ventriculograms in the right

anterior oblique projection were analyzed by planimetry of the aneurysmal and non aneurysmal areas This method provided data favorably altered by surgery in the improved patients and unchanged in the others None of the preoperative ventriculographic measurements effectively separated the postoperative patient groups The poor results in the Group 2 patients were of heterogeneous origin arising from pre , peri and postoperative factors The more important factors were the largest and smallest aneurysms, surgically induced mitral insufficiency, and progressive coronary artery disease Thus the improvement in surgical results from better angiographic preoperative case selection is possible, but limited

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Coronary artery to pulmonary artery fistulas

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Congenital coronary artery fistulas are rare but well known clinical entities [8] These fistulas may drain into the low pressure right heart chambers the coronary sinus the pulmonary artery the bronchial circulation and left atrium and very rarely the left ventricle According to the site of drainage these fistulas may present with characteristic continuous murmurs and occasionally may be confused with patent ductus arteriosus [6] Recent reports postulate that small coronary fistulas may be the result of severe obstructive coronary artery disease [9] with the fistulas originating proximal to a severe coronary obstruction The purpose of this report is to discuss our experience with 12 patients having coronary artery to pulmonary artery fistulas discovered during routine coronary arteriography in the past ten years

Material and results

The twelve patients were discovered during diagnostic coronary arteriography performed at our institution The clinical data of these patients is presented in Table I Patient No 1 was studied because of the presence of continuous murmur thought to be patent ductus arteriosus Patient No 7 was studied for evaluation of rheumatic heart disease Ten patients were studied for the evaluation of chest pain suspected to be angina pectoris there were three women and nine men with an age range of 35 to 70 years and an average age of 61 years The ECG was normal in five patients showed left ventricular hypertrophy in two patients and in five patients there were ST segment and/or T wave abnormalities The left ventricular end diastolic pressure was normal (less than 12 mm Hg) in eight patients Indicator dilution curves with injection of Cardiogreen into the pulmonary artery and sampling in the aorta were obtained in all patients and were normal Hydrogen studies performed in two patients were negative Six patients had severe coronary artery disease (one vessel disease in two patients two vessel disease in one patient and three vessel disease in three patients) One patient had insignificant coronary artery disease (less than 50 per cent narrowing) One patient had rheumatic heart disease (mitral stenosis and insufficiency and aortic insufficiency) and six patients had normal coronary angiograms

There were 14 fistulas in the 12 patients ten fistulas originated from the proximal left anterior descending artery three from the proximal right coronary artery and one from the *proximal left* circumflex artery In only four of the six patients with severe coronary artery disease the donor vessel (i e the vessel from which the fistula originates) was involved with significant narrowing In the remaining two patients the donor vessel was not involved and the *atherosclerotic* narrowing was limited to the other vessels Angiographically the fistulas could be divided into two types

1 The fistula consisted of one large channel (Fig 1) or one or more small (Fig 2) but discrete channels In each case the contrast media was clearly seen spurting into the main pulmonary

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Received for publication Dec 27 1977
Accepted for publication Feb 13 1978
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Table 1 Clinical hemodynamic and angiographic data in 12 patients with coronary artery to pulmonary artery fistulas

Patient no initials age & sex	Coronary arteriography % narrowing				Origin of fistula	Type of fistula	Continuous murmur	ECG	LVEDP (mm Hg)	Dye dilution	H_2 study	Reason for study
	LM	LAD	LCF	RCA								
1 I F 40 M	0	0	0	0	LAD	Many small channels	+	LVH	10	N	Not done	Continuous murmur
2 L W 46 M	0	0	0	0	LAD	Single large channel	–	LAH ST T	12	N	(–)	Angina
3 O W 57 M	0	0	40%	40%	LAD RCA	Single small Single small	–	N	10	N	Not done	Atypical angina
4 S C 47 F	0	70%	100%	100%	LAD RCA	Single large Single large	–	IRBBB ST T	20	N	Not done	Angina
5 J G 70 M	95%	0	80%	0	RCA	Single small	–	ST T	8	N	Not done	Angina
6 G K 45 F	0	0	0	0	LAD	Single large	–	N	10	N	Not done	Atypical angina
7 M B 59 F	0	0	0	0	LCF	Two small	–	LVH A F	11	N	Not done	R H D
8 J F 35 M	0	0	0	0	LAD	Single large	–	ST T	12	N	Not done	Angina
9 P W 53 M	0	0	0	0	LAD	Single small	–	N	20	N	Not done	Atypical angina
10 J M 54 M	0	99%	90%	100%	LAD	Single small	–	LAH ST T	9	N	Not done	Angina
11 F W 54 M	0	70%	80%	99%	LAD	Plexiform	+	N	25	N	(–)	Angina
12 F T 58 M	0	100%	0	0	LAD	Plexiform	–	N	17	N	Not done	Angina

Abbreviations M male F female LM left main coronary artery LAD left anterior descending artery LCF left circumflex artery RCA right coronary artery LVEDP left ventricular end diastolic pressure N normal LVH left ventricular hypertrophy LAH left anterior hemiblock ST T ST segment and T wave abnormalities IRBBB incomplete right bundle branch block AF atrial fibrillation RHD rheumatic heart disease

artery This type was seen in 12 fistulas in the presence or absence of obstructive coronary artery disease

2 The fistula was composed of a plexiform arrangement of vessels (Fig 3) This type was seen in two patients both with significant coronary artery disease

There was no proximal dilatation of the donor vessel in any case Patient No 1 underwent ligation of the fistula and the angina disappeared following surgery Patient No 11 underwent ligation of the fistula with triple saphenous vein bypass surgery for the associated coronary artery disease In each patient the fistula was suture ligated near the anastomosis with the pulmonary artery and the thrill which was felt over the pulmonary artery before ligation disappeared following the ligation

Discussion

Coronary artery fistulas are anomalies due to defective development of the coronary circulation during fetal life[10] They originate from the major coronary vessels and drain in the low pressure right cardiac chambers commonly into the right ventricle and less frequently into the right atrium, coronary sinus pulmonary artery, bronchial circulation and very rarely into the left atrium and left ventricle[1,9] The coronary artery involved is usually tortuous and markedly dilated[2] The basic pathophysiologic abnormality of this disorder is left to right shunt, the magnitude of which will be influenced by the functional size of the opening of the fistula at the point of distal communication and other factors, such as systemic and pulmonary artery pressures[4] The fistulas may drain with the single opening or with multiple openings in the form of plexiform vessels Most of the patients present with characteristic continuous murmur located in areas other than the usual location of the continuous murmur of the patent ductus arteriosus The location of the murmur is dependent upon the site of drainage of the fistula In several patients the

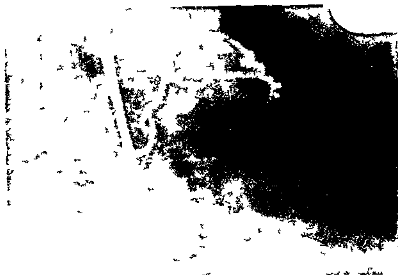


Fig 1 Selective right coronary arteriogram in the right anterior oblique projection showing a discrete and relatively large fistula arising proximal to total occlusion of the vessel and draining into the pulmonary artery

correct diagnosis was made during surgery for suspected patent ductus arteriosus The majority of the patients are asymptomatic for many years and symptoms occur usually in the older age group as a result of the long standing shunt or the development of obstructive coronary artery disease or systemic hypertension The complications may include congestive heart failure angina pectoris due to coronary steal and bacterial endocarditis

Recent reports indicated that coronary fistulas may exist without clinical manifestations and are discovered during diagnostic coronary arteriography The reported cases were associated with significant obstructive coronary artery disease [9] and the authors considered them as being acquired secondary to the coronary obstructions In two patients the fistulas were reported to originate from the right coronary artery and drained into the right atrium In the third patient the fistula originated from the left anterior descending artery and drained into the great cardiac vein In the fourth patient the fistula originated from the left anterior descending and drained into the left atrium [9] All these fistulas were small silent and originated proximal to a severe obstruction of the diseased vessel All the fistulas were interrupted during aortocoronary bypass surgery for the obstructive coronary disease

In our study we have chosen only those fistulas which drain into the pulmonary artery and because of the anatomic location such fistulas should be easily detected during coronary arteriography

We found 14 fistulas in 12 patients (two patients had two fistulas each) Ten fistulas originated from the left anterior descending artery three from the right coronary artery and one from the left circumflex artery Five fistulas were composed of one large channel in each (Fig 1) seven fistulas were composed of one or more small but discrete channels (Fig 2) Two fistulas were formed of plexiform arrangement of channels (Fig 3) In each case contrast material was clearly seen spurting into the pulmonary artery during selective coronary arteriography In four out of six patients with coronary artery disease the donor vessel was involved with significant narrowing and in each case the fistula originated proximal to the lesion There was no proximal dilatation of the coronary artery in any of the 12 patients The plexiform arrangement of fistulas was only seen in the presence of coronary artery disease however the discrete variety was seen in both normal subjects and in patients with coronary artery disease

Two of our patients had characteristic continuous murmurs one patient had a normal coronary angiogram and the second had severe coronary artery disease

Hydrogen study was performed in two patients and was normal in each Dye dilution curves performed in all patients were normal It has been suggested that fistulas are visualized only because of the pressure of injection during coronary



Fig 2 Selective left coronary arteriogram in the right anterior oblique projection showing small but discrete fistulas arising from the proximal left anterior descending artery and draining into the pulmonary artery The left circumflex artery is totally occluded

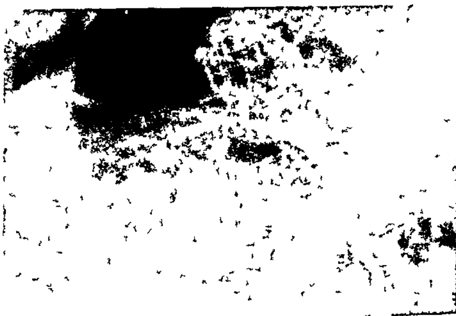


Fig 3 Selective left coronary arteriogram in the left lateral projection showing a plexiform arrangement of coronary artery to pulmonary artery fistulas arising from the left anterior descending artery just proximal to its total occlusion

arteriography and may very well be functionally closed at other times[7] Although this tends to substantiate the negative hydrogen studies and normal dye dilution curves in our patients it does not explain the finding of a thrill over the pulmonary artery in two patients who underwent ligation of the fistulas We rather believe that the amount of shunt was small and that there is definite limitation of the above techniques in shunt detection Recently, Blau and associates[11] have used 99mTc albumen particles for a semiquantative estimation of the shunt in a patient with coronary artery fistula

The pathogenesis of these fistulas is unknown Probably they represent a spectrum of a developmental defect during fetal life as are the more classic forms of congenital coronary fistulas The fact that half of our patients did not have obstructive coronary artery disease suggests that the coronary obstruction is not responsible for the

development of the fistulas The functional significance of this type of fistula is uncertain The presence and magnitude of coronary steal in our patients could not be answered from this study The recent interest in myocardial imaging with Thallium 201 both at rest and during exercise may be useful in helping to make decisions about management of these patients A perfusion deficit in the region of distribution of the donor vessel may be an indirect indication of coronary steal particularly in patients with normal coronary arteries

In summary we have described 12 patients with coronary artery to pulmonary artery fistulas both in the presence and absence of obstructive coronary artery disease We have no evidence to substantiate that obstructive coronary artery disease may cause coronary fistulas We found no different morphologic or functional characteristics of the coronary fistulas with or without coronary obstructions Their etiology therefore must be assumed to be congenital Although in the majority of patients with otherwise normal coronary arteries the functional significance of the fistulas is not important the development of obstruction may aggravate the perfusion deficit because of the coronary steal

Summary

Twelve patients with a total of 14 coronary artery to pulmonary artery fistulas were discovered at the time of diagnostic coronary angiography Six patients had severe coronary artery disease five patients had normal coronary arteriography one patient had insignificant coronary artery disease and one patient had rheumatic heart disease Only two patients had characteristic continuous murmurs one patient had a normal coronary angiogram and the second patient had severe coronary artery disease Ten fistulas originated from the left anterior descending artery three from the right coronary artery and one from the left circumflex artery The fistulas were either composed of one large (five fistulas) or one or more small channels (seven fistulas) or poorly defined plexiform channels (two fistulas) Hydrogen studies performed in two patients were negative and dye dilution curves performed in all patients were normal In only four out of the six patients with severe coronary artery disease the fistulas originated from a diseased vessel and in each case the origin was proximal to the narrowing The pathogenesis and functional role of these fistulas is largely unknown

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Migraine and the mitral valve prolapse syndrome

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The mitral valve prolapse syndrome occurs in about 6 per cent of young women[1] Clinical reports of this syndrome have emphasized the cardiac manifestations of a mid systolic click with or without a mid to late systolic murmur and the usually associated symptoms of atypical chest pain, dyspnea, fatigue, and palpitations Observations regarding secondary neurological symptoms are generally limited to descriptions of light headedness, dizziness syncope, and frequently undescribed 'psychoneurotic complaints[2] During the course of our evaluation of patients with prolapse of the mitral valve, we discovered a remarkably high incidence of migraine syndrome in these patients This report comprises our evaluation of the association of migraine and the mitral valve prolapse syndrome

Material and methods

A retrospective study was conducted on 230 patients with mitral valve prolapse syndrome seen during the past four years for cardiac or neurological evaluation Complete history and physical examinations were carried out The diagnosis of mitral valve prolapse was made by the presence of the typical mid to late systolic click with or without a late systolic murmur In those few patients in whom no physical findings were present, classic echocardiographic criteria and/or angiographic findings of mitral valve prolapse were present Two hundred twenty two patients had echocardiographic studies[3] Ten patients had cardiac catheterization studies at Akron General Medical Center Two other patients had catheterization studies elsewhere, and these were reviewed personally Where deemed necessary because of severe neurological symptoms additional studies such as electroencephalogram skull x rays radionuclide brain scans and computerized tomography were done

Sixty four of the 230 patients or 28 per cent were identified as having symptoms characteristic of migraine Included were symptoms such as throbbing, pulsating headache, teichopsia visual scotoma, and transient neurological deficits that were repetitive in young people, such as hemiparesis Individual migraine syndromes were classified according to the criteria of the Ad Hoc Committee on Headache of the National Institute of Neurological Diseases and Blindness[4]

Results

There was a marked preponderance of Caucasian females in our patient group (Table I) The majority of patients had the onset of migraine during the second and third decades of life (Table II) The most frequent types of migraine encountered were the common and classic varieties (Table III)

Most patients had both physical examination and echocardiograms positive for the prolapse mitral valve syndrome (Table IV) In ten patients however the physical examination was negative Of these, nine had classically positive echocardiographic findings of mitral valve prolapse, and one had angiographic demonstration at cardiac catheterization

Illustrative case report

V C a 33 year old white woman was referred for evaluation of episodic visual loss and head

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Received for publication Feb 27 1978
Accepted for publication Apr 28 1978

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Table I Sex and race of 64 patients with diagnosis of migraine and prolapsed mitral valve

Female	59	92%
Male	5	8%
White	61	95%
Black	3	5%

Table II Age of onset of migraine in 64 patients with diagnosis of migraine and prolapsed mitral valve

Age of onset (yrs)	*Total patients—64*
0-10	3
11 20	27
1 30	22
31-40	7
41 0	5

ache These began at age 26 and started with large blotches of darkness in both eyes Her left eye gradually became blind Simultaneously she noted brief flashing lights described as an ex ploding firecracker in her right eye also followed by blindness These episodes lasted about ten minutes and were followed by the onset of a severe throbbing headache usually beginning behind the left eye and in the left temporal area accompanied by return of vision Nausea and vomiting were frequent She often had a similar headache without premonitory symptoms

For several years she had experienced intermit tent left lateral chest discomfort The pain was described as sharp and located just to the left of the sternum at the sixth and seventh ribs The pain did not radiate and lasted ten minutes to two hours Palpitations were frequent A cardiac murmur was first heard at age six but had not been investigated

She had "convulsions until the age of 12 Her mother had severe migraine headaches and a younger brother had been thought to have rheu matic fever elsewhere on the basis of cardiac examination Her older brother had at least one episode of similar visual loss

Cardiac examination revealed a normal apex impulse First and second sounds were normal with a classic midsystolic click and late systolic murmur heard best in the left lateral decubitus position No diastolic murmur was present (Fig 1) Rare premature ventricular beats were heard

Table III Classification of migraine in 64 patients with diagnosis of migraine and prolapsed mitral valve

Type of migraine	*No*
Common	42
Classic	12
Common and classic	1
Common and paratrigeminal	1
Cluster	2
Hemiplegic	5
Ophthalmoplegic	1

Table IV Physical and ECHO findings in 62 patients with diagnosis of migraine and prolapsed mitral valve

Click of click murmur noted	54	84%
No click or murmur	10	16%
Total positive ECHO	47	73%

Of these 10 patients, nine had positi e echoes and one had posit ve cineangiogram f r mitral val e p olapse

Blood pressure was normal Neurological exami nation was normal

Resting ECG, chest x ray and routine labora tory studies were normal A 24 hour Holter moni tor showed only unifocal ventricular premature beats Echocardiographic evaluation (Fig 2) demonstrated mitral valve prolapse

Neurological studies including electroencepha logram brain scan, and skull x rays were normal

She was treated with gradually increasing doses of propranolol ultimately to 160 mg per day Chest pain and palpitations were rare at this level. Visual symptoms and headache were completely eliminated

Discussion

To our knowledge this is the first reported association of these two syndromes Prevalence of migraine among the female population is said to be about 10 per cent[5] In our study 28 per cent of patients with mitral valve prolapse also had migraine Although these were unselected pa tients this was not a randomized study since all patients were referred for either a cardiac or neurological evaluation Only a large population study completely randomized can ultimately confirm or deny our conclusions regarding the association of the two syndromes

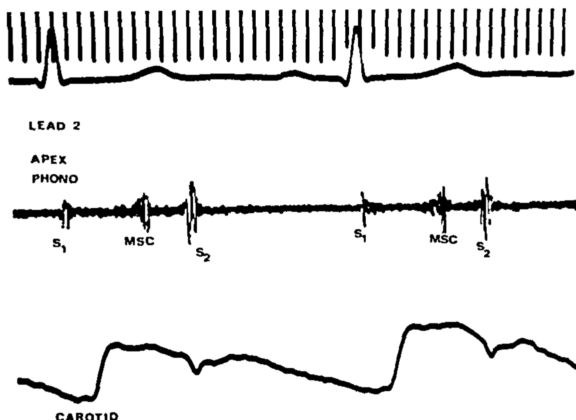


Fig 1 Phonocardiogram demonstrated midsystolic click *(MSC)* recorded at the apex

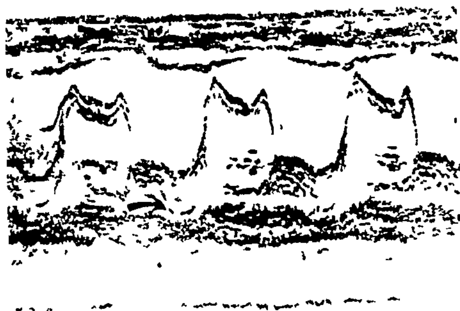


Fig 2 Echocardiogram reveals classic midsystolic prolapse of mitral valve *(see arrow)*

Certain clinical features in both groups suggest a raltionship between migraine and the prolapse valve syndrome Both are more common in women Paroxysmal tachycardia, syncope light headedness vertigo and chest pain have been linked to migraine and are well known in the mitral valve prolapse syndrome Propranolol a beta blocking agent has been an effective drug in reducing the symptoms and arrhythmias of the mitral valve prolapse syndrome [6] This same agent has been uniformly and impressively utilized for the treatment and prevention of migraine in our patient group This drug has been so effective that it has become our first choice in treatment of migraine

Recently Barnett and associates from London

Ontario[7] documented transient ischemic attacks and completed strokes in patients with the mitral valve prolapse syndrome Several of these patients appear to have had emboli as a pathophysiologic mechanism In the past four years we have recognized four patients with neurological disorders that we consider to be secondary to emboli from a prolapsed valve

The reasons for emboli forming on this valve are unclear particularly in the absence of an associated endocarditis Pathological changes on the margin of the prolapsed valves as described by Pomerance and by Silver may initiate platelet adherence and aggregation and a platelet fibrin thrombus eventually may form become detached and may cause embolic infarction

Multiple reports have also stressed an increased incidence of stroke in patients with migraine especially those with complicated migraine[6] Migraine patients are known to demonstrate platelet hyperaggregability Although vasospasm is usually cited as the cause of strokes associated with migraine the role of hyperaggregability of platelets in those strokes has not yet been investigated Indeed if as we suggest these two syndromes are related this abnormality of platelet function could play a basic role in the origin of emboli from the abnormal mitral valve Some manifestations of the migraine syndrome may in fact be a result of repetitive emboli from the mitral valve Kalendovsky and Austin[3] suggested the possibility of an association between platelet hyperaggregability and neurologic symptoms of migraine Support for this concept comes from a recent report by Caplan and co workers of the new onset of migraine syndrome occurring after insertion of a prosthetic cardiac valve More recently however Couch and Hassanein have denied that symptoms of migraine are related to platelet aggregation but did suggest that the increased incidence of thrombotic stroke in migraine subjects could be due in part to platelet hyperaggregability Weksler and associates recently demonstrated that propranolol added to platelets in vitro inhibited platelet aggregation induced by ADP epinephrine collagen and thrombin

We believe it is most important for the physician to recognize the association of these syndromes All patients with migraine syndrome should be evaluated to determine the presence or absence of mitral valve prolapse If the latter is recognized then consideration should be given to providing subacute bacterial endocarditis prophylaxis Endocarditis represents a well known complication of mitral valve prolaspe syndrome On the other hand in patients with mitral valve prolapse seeking out the symptoms of migraine may prevent the prescription of birth control pills which might precipitate severe migraine or even strokes in susceptible patients

Summary

We believe there is a significant association between migraine and the prolapse mitral valve syndrome Propranolol is the drug of choice in these patients for the treatment and prevention of migraine Increased platelet aggregability may be the common pathophysiologic mechanism as relates to emboli from the valve and possibly in strokes related to migraine Recognition of the association of the two syndromes will result in appropriate subacute bacterial endocarditis prophylaxis for patients at risk as well as prevention of improper medication to those patients with migraine who are at risk for stroke

This paper was presented in part on September 23 1977 at the Fifth Annual Combined Meeting of the Ohio Chapter of the American College of Physicians and the Ohio Society of Internal Medicine Kings Island Ohio

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Experimental and laboratory reports

The ventricular A wave: a new echocardiographic index of late diastolic filling of the left ventricle

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In the normal heart, left ventricular filling takes place predominantly during early and late diastole with little filling occurring during mid diastole.[1,2] In the hypertrophied ventricle, however, it has been demonstrated that early filling is impeded. This is reflected by a reduction in the "y" descent of the left atrial pressure trace and by a decrease in the E-F slope of the anterior mitral valve leaflet seen on echocardiography.[5-7] The precise cause of decreased early filling in left ventricular hypertrophy is not known, but it may be related to decreased left ventricular compliance.[8] To insure adequate left ventricular filling, atrial contraction becomes more forceful and prolonged, augmenting the amount of filling in late diastole.[7]

Echocardiography has been a useful tool in the evaluation of left ventricular function, especially in the absence of asynergy. Although echocardiographic correlates of early diastolic filling[6] have previously been described, there has been little emphasis on abnormalities of late diastolic filling. Therefore, in order to study the late diastolic filling period, we have measured the changes in left ventricular internal diameter occurring at end-diastole in patients with and without left ventricular hypertrophy.

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Received for publication N[illegible] 1, 1977.
Accepted for publication Dec. 19, 1977.

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Methods

From the population of patients studied in our non-invasive laboratory, 30 normal volunteers (group A), 25 consecutive patients with left ventricular hypertrophy (secondary to aortic stenosis, idiopathic hypertrophic subaortic stenosis, or hypertension) and normal sinus rhythm (group B), and 15 patients with atrial fibrillation (group C) in whom the endocardial surfaces of the left ventricular posterior wall and interventricular septum could clearly and precisely be defined were studied by standard time-motion echocardiography. All patients with abnormal septal motion were excluded. Echocardiographic criteria for left ventricular hypertrophy consisted of a posterior wall and/or interventricular septum > 11 mm. In addition, 23 of 25 patients of group B had some other evidence of left ventricular hypertrophy either on electrocardiogram[15] or by angiography.[8] No patient in group B had known rheumatic mitral valve disease or mitral valve prolapse. In group C (atrial fibrillation) three patients had mitral stenosis, three had left ventricular hypertrophy, two had atrial fibrillation alone, six had mitral stenosis and left ventricular hypertrophy, and one had a mitral valve prosthesis.

All patients were examined supine or in the left lateral decubitus position. A Unirad echocardiograph and either a 10 mm diameter 2.25 mHz 7.5 or 10 cm focused or unfocused transducer was used for all the echocardiograms which were recorded on Honeywell or Tektronix recorders. Each echocardiogram was evaluated indepen-

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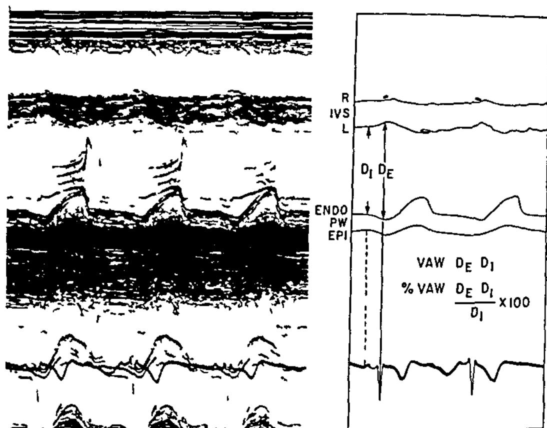


Fig 1 Echocardiogram of a normal individual (group A) *At right* schematic representation showing methods of measurement to calculate the VAW *IVS* = interventricular septum *L* = left side of IVS *R* = right side of IVS *PW* = posterior wall of left ventricle *Endo* = endocardium of PW *Epi* = epicardium of PW D_I = initial internal diastolic dimension of the left ventricle D_E = end diastolic dimension of the left ventricle *VAW* = ventricular A wave

Table I Summary of echocardiographic data*

Group	*A*	*p*	B_1	*p*	*B*
Number	30		19		6
PR AC interval (sec)	Normal (> 06 sec)		Normal (> 06 sec)		Abnormal (< 06 sec)
Age (years)	34 5 ± 2 0	<0 001	53 3 ± 3 8	NS	57 5 ± 4 0
Heart rate (per min)	68 5 ± 1 5	NS	69 0 ± 2 7	NS	68 4 ± 4 1
LA size (cm /M ²)†	1 7 ± 0 1	NS	1 9 ± 0 1	NS	2 5 ± 0 2
PW thickness (mm)	9 6 ± 0 2	<0 001	13 8 ± 0 6	NS	14 4 ± 1.2
IVS thickness (mm)	10 0 ± 0 7	<0 001	15 3 ± 0 7	NS	15 6 ± 0 9
E F slope (mm /sec)	103 0 ± 4 3	<0 001	50 5 ± 5 3	NS	55 0 ± 12 7
D_I (cm)	4 3 ± 0 2	NS	3 9 ± 0 1	NS	4 3 ± 0 4
Ejection fractions (%)	65 0 ± 1 9	NS	67 0 ± 2 6	NS	61 0 ± 4.8
PR interval (sec)	0 17 ± 0 01	NS	0 19 ± 0 04	NS	0.20 ± 0 02

The values are expressed as the mean ± the standard error of the mean
†Abbreviations LA = left atrial PW = posterior wall IVS = interventricular septum DI = initial internal diastolic LV dimension

dently by at least two observers with less than 10 per cent variation in these interpretations

Four patients from group B_1 *(see below)* had additional echocardiograms performed during right ventricular pacing at heart rates just above their own intrinsic rate In addition 15 subjects from all groups had repeat echocardiograms for evaluation of reproducibility of measurements

The following parameters were measured on each echocardiogram Left atrial size the E F slope of the anterior mitral valve leaflet (the E F slope was measured when present") the PR minus AC interval of the mitral valve " diastolic interventricular septal and left ventricular posterior wall thickness measured before atrial systole and diastolic and systolic internal dimensions of

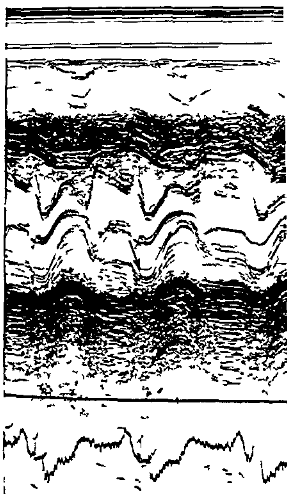


Fig 2 Echocardiogram of a patient with idiopathic hypertrophic subaortic stenosis (group B) showing a large VAW *(arrow)* In addition note the presence of posterior wall hypertrophy

the left ventricle Systolic and diastolic left ventricular volumes and ejection fractions were calculated On the basis of the PR minus AC interval group B was subdivided into group B_1 (19 patients) who had a normal PR minus AC interval (> 0 06 sec) and group B (six patients) with a large notch on the A C slope and a shortened PR minus AC interval (< 0 06 sec)

Diastolic dimensions of the left ventricle were measured just below the mitral valve or where the posterior leaflet of the mitral valve was seen An initial left ventricular late diastolic internal dimension (D) was measured at the beginning of the P wave of the electrocardiogram and an end diastolic internal dimension (D_E) was measured at the peak of the R wave of the QRS complex at

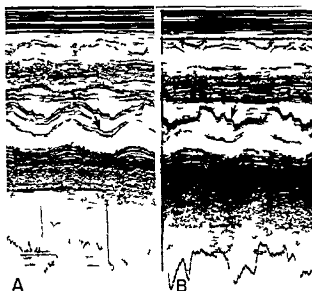


Fig 3 Echocardiogram of a patient in group B with hypertensive heart disease demonstrating *(A)* significant symmetric left ventricular hypertrophy and a small VAW *(arrow)* and *(B)* a marked notch on the A C slope of the anterior mitral valve leaflet *(arrow)*

a time when the interventricular septum dipped anteriorly and the posterior wall moved posteriorly (see Fig 1) At least three complexes were averaged to determine the diastolic diameters of the left ventricle In patients in atrial fibrillation the D_I was arbitrarily measured 160 msec before the QRS complex

The absolute difference between these two diastolic dimensions (D_E D_I) was defined as the ventricular A wave (VAW) and the per cent ventricular A wave (per cent VAW) normalized for D_I was measured as $D_E - D_I/D_I \times 100$ Statistical analyses were performed using the Student s t test

Results

The results of the echocardiographic measurements in groups A B and B_2 are given in Table I Representative echocardiograms from each of the groups are shown in Figs 1 2 and 3

When compared to group A the patients in groups B_1 and B_2 were older had increased posterior wall and interventricular thickness and decreased E F slopes (Table I) Even though the PR intervals were longer and their left atria larger the differences between these groups were not significant The left ventricular diastolic dimensions and ejection fractions were also similar between the groups The VAW and per cent

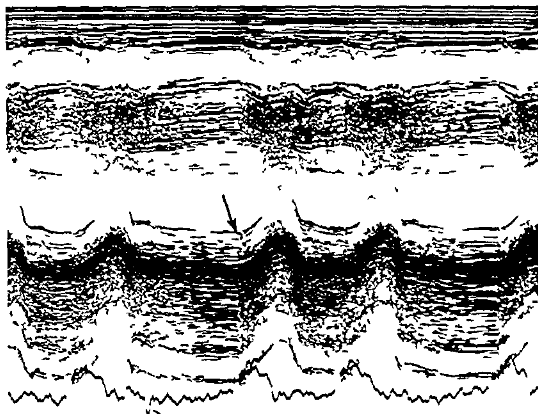


Fig 4 Echocardiogram of a patient with left ventricular hypertrophy and atrial fibrillation (group C) showing an absent VAW *(arrow)*

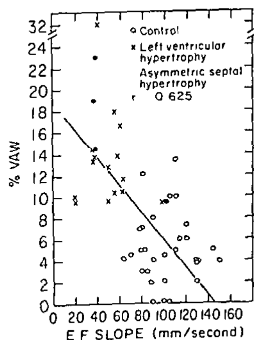


Fig 5 Per cent ventricular A wave in relation to the E F slope of anterior mitral valve leaflet in normal individuals (group A) patients with left ventricular hypertrophy and patients with asymmetric septal hypertrophy (Group B)

VAW for these groups are shown in Table II

The VAW and per cent VAW of group B_1 were statistically greater than in groups A and B_2 There were no statistical differences between groups A and B_2 Although the age of the controls was significantly less than in group B_1 eight control patients over the age of 35 (mean age of 46) had a per cent VAW of 6 1 per cent which was not significantly different from the rest of the control group (group A) With atrial fibrillation (group C), the per cent VAW was markedly smaller than in the normals, even if left ventricular hypertrophy was present (Table II and Fig 4)

Comparison of VAW with other echocardiographic parameters In groups A and B_1 there was a weak inverse relationship between the E F slope of the anterior mitral valve leaflet (as an index of early diastolic filling) and the per cent VAW (r value = −0 63) (Fig 5) However, 18 of the 19 patients in group B_1 had a reduced E F slope of the anterior mitral valve leaflet (< 70 mm /sec) On the other hand a direct correlation between the degree of hypertrophy and the per cent VAW was present, slightly better with interventricular septal thickness (r = 0 74) than with posterior wall thickness (r = 0 70) (Fig 6) No correlation between these parameters was found in the other groups

The VAW and right ventricular pacing To further evaluate the relation of the VAW to atrial contraction four patients in group B_1 had echocardiograms performed during right ventricular pacing The VAW disappeared during pacing and

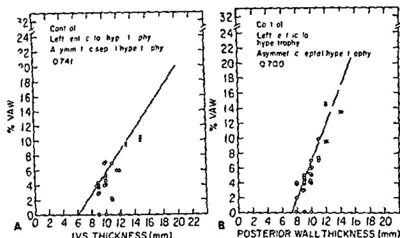


Fig 6 Per cent ventricular A wave in relation to *(A)* interventricular septal thickness and *(B)* left ventricular posterior wall thickness, in normal individuals (control) patients with left ventricular hypertrophy and patients with asymmetric septal hypertrophy (group B)

Table II Summary of VAW data

Group	*A*	*p*	*B*	*p*	*B*	*C*
VAW (cm.)	0.23 ± 0.03	< 0.001	0.51 ± 0.03	< 0.001	0.22 ± 0.07	0.06 ± 0.04
% VAW	4.9 ± 0.6	< 0.001	14.5 ± 0.5	< 0.001	4.9 ± 1.6	0.5 ± 0.3

Abbreviations VAW = ventricular A wave

reappeared during normal conduction or when atrial contraction preceded pacemaker activation of the left ventricle (Figs 7 and 8)

Reproducibility In the 15 subjects of this study who had a repeat echocardiogram to evaluate the reproducibility of our measurements we found no significant differences in the magnitude of the VAW

Discussion

The echocardiogram of the normal left ventricle during end-diastole shows a posterior motion of the endocardial surface of the posterior wall and an anterior motion of the interventricular septum The significance of these movements has not been well studied In 1970 Kraunz and Kennedy [9] divided the precontraction dip of the posterior left ventricular wall into a late diastolic and an early systolic component The late diastolic posterior motion was attributed to atrial contraction while the systolic component was assumed related to isovolumetric contraction This increase in the left ventricular diameter during isovolumetric contraction has also been seen by ventriculography [2]

The importance of atrial contraction in late diastolic filling of the left ventricle was first recognized by Harvey [22] Although subsequent investigators have differed on the actual contribution of atrial contraction to left ventricular filling in the normal heart most studies have shown that on the average 20 to 35 per cent of filling occurs during this period [23-25] The major determinants governing the amount of late diastolic filling are the presence of a normal mitral valve the force and timing of atrial contraction and the pressure-volume relationship of the left ventricle [26]

The larger VAW and per cent VAW in patients with left ventricular hypertrophy and a normal PR minus AC interval (group B_1) than in normal individuals indicates enhanced late diastolic filling subsequent to atrial contraction in these patients These differences were independent of PR interval left atrial and left ventricular size (see Table I) The weak inverse relationship between the E F slope of the anterior mitral valve leaflet and the per cent VAW suggests that as early diastolic filling decreases reflected in a decrease in the E F slope late diastolic filling is augmented in order to maintain a normal stroke volume This type of relationship has also been found in patients with hypertrophic cardiomyopathy and coronary artery disease [3, 27] by angio

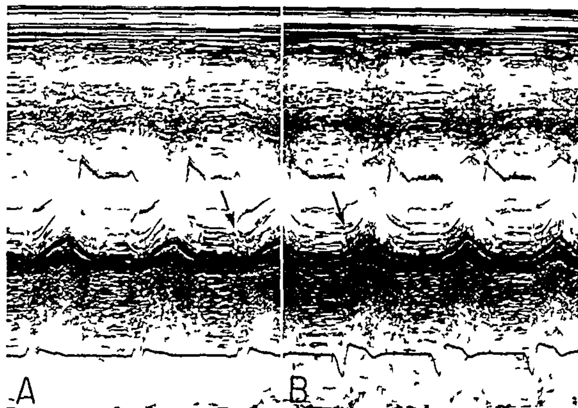


Fig 7 Echocardiogram of a patient with left ventricular hypertrophy *A* During sinus rhythm a VAW is present *(arrow)* *B* Same position as in *A* The VAW is absent *(arrow)* during right ventricular pacing at a slightly faster rate than in *A*

graphic studies In patients with aortic stenosis, Stott and colleagues[10] observed an increase in the left ventricular circumference during atrial systole in addition to augmented left ventricular filling occurring during this period This further ventricular enlargement in diastole observed after atrial contraction is consistent with the larger VAW we observed in our patients with left ventricular hypertrophy With atrial fibrillation or during ventricular pacing the VAW significantly decreased or disappeared respectively, confirming its relation to atrial contraction

The increased end diastolic pressure at a normal end diastolic volume seen in patients with left ventricular hypertrophy has been attributed to abnormal left ventricular compliance [28,29] Grossman and associates,[30] using simultaneous left ventricular pressure and echocardiographic volume measurements, found an exaggerated increase in pressure relative to change in volume at end diastole in patients with left ventricular hypertrophy Although simultaneous pressures were not measured in our study, we believe that the ability of the hypertrophied ventricle to expand in end diastole as demonstrated echocardiographically (group B_1) suggests that an increase in end diastolic filling may partially be responsible for elevations of end diastolic pressure in left ventricular hypertrophy In another study, Grossman and co workers[31] have also shown a relationship between the degree of diastolic stiffness and left ventricular wall thickness In our study we have shown a relationship between the VAW and posterior wall on interventricular septal thickness, suggesting that late diastolic filling depends to some extent on the degree of hypertrophy

The significantly smaller VAW in group B_2 (left ventricular hypertrophy and delayed mitral valve closure) than in group B_1 (left ventricular hypertrophy and normal mitral valve closure) suggests less of an increase in left ventricular size with atrial contraction in the former group Along with the decreased E F slope of the anterior mitral valve leaflet, it would indicate impaired left ventricular filling throughout diastole while in group B_1 left ventricular filling is decreased only in early diastole

A delayed mitral valve closure as seen in group B_2 has been related to an exaggerated increase of left ventricular end diastolic pressure[11] and/or an abnormal left ventricular dp/dt [32] These parameters probably reflect left ventricular dysfunction with greater chamber stiffness in group B_2

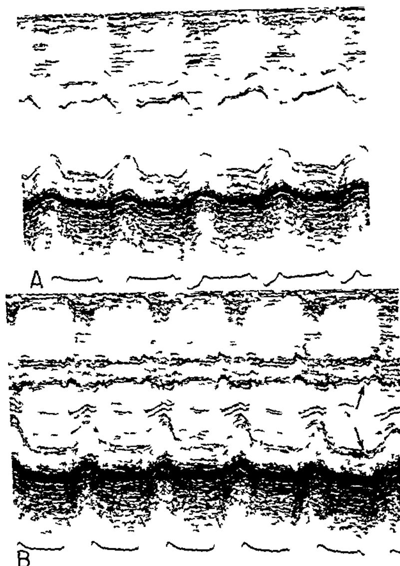


Fig 8 Echocardiogram of a patient with left ventricular hypertrophy demonstrating *(A)* the presence of a VAW during sinus rhythm and *(B)* its disappearance during right ventricular pacing and its reappearance when a P wave precedes the ventricular activation *(arrow)*

It should be noted that there are several limitations to the assessment of any echocardiographic measurement of the left ventricle We assume that the ice pick view of the left ventricle obtained with the echocardiographic beam is representative of the entire chamber provided there is no regional left ventricular asynergy We presumed normal left ventricular contraction in all our normal volunteers Thirteen of the 25 patients in group B had normal and uniform ventricular contraction on left ventriculography in 10 of the other 12 patients there was no clinical suggestion of left ventricular asynergy (i.e no history of myocardial infarction and no abnormal Q waves in the electrocardiogram) although angiography was not performed

Only patients with adequate echocardiograms for the identification of left ventricular wall layers were included implying other limitations of this type of assessment Approximately 30 per cent of the echocardiograms evaluated for this study were rejected because of inadequate images Even in the adequate echocardiograms utilized important errors can result from problems in ultrasonic resolution Different beam widths or gain control settings may give an error

in echocardiographic measurements in the order of 1 to 2 mm In addition, in some individuals it may be impossible to discern the endocardium from other echoes (i e , chordal structures papillary muscle) Furthermore, we arbitrarily chose the peak of the R wave of the electrocardiogram to define end diastole although it may actually precede or follow this point by 0 01 or 0 02 sec The peak of the R wave did not always coincide with the largest left ventricular diastolic diameter However, the magnitude of the VAW by inspection of each echocardiogram was obviously larger in group B_1 compared to the other groups and we feel that these measurements reflect real changes in end diastolic volumes In spite of these limitations and the fact that our study is based on small differences in the VAW between the different groups, we were able to reproduce these measurements in the subjects with duplicate echocardiograms

In conclusion, our findings suggest that echocardiography might provide a unique, non invasive method to follow patients with left ventricular hypertrophy, especially secondary to hypertension, aortic stenosis, and idiopathic hypertrophic subaortic stenosis Not only is it an accurate indicator of left ventricular wall thickness [33,34] but it also is sensitive in demonstrating impaired left ventricular filling in early diastole (as measured by a decreased E F slope of the anterior mitral valve leaflet) as well as reflecting the increased filling in late diastole (a large VAW) In most patients with left ventricular hypertrophy, there is a decrease in the E F slope of the anterior mitral valve leaflet with a large VAW With progression of the left ventricular hypertrophy, perhaps the ventricle becomes more stiff resulting in impaired late diastolic filling (decreasing VAW) with delayed mitral valve closure in addition to the decrease in early diastolic filling This stage probably precedes significant dilatation of the left ventricle Future studies evaluating the VAW in patients with left ventricular volume overload (in contrast to our patients with left ventricular pressure overload) and adding hemodynamic and clinical data will be required to support these conclusions

Summary

Echocardiography was used to evaluate the late diastolic filling period of the left ventricle in 30 normal individuals 25 patients with left ventricular hypertrophy, normal sinus rhythm and either a normal or delayed mitral valve closure, and 15 patients with atrial fibrillation The echocardiographic ventricular A wave (VAW) was defined as the difference between the end diastolic and an earlier late diastolic internal left ventricular dimension and it was felt to primarily reflect the atrial contribution to late diastolic filling of the left ventricle It disappeared during ventricular pacing and was significantly smaller than normal in patients with atrial fibrillation The VAW was significantly larger in patients with left ventricular hypertrophy and normal mitral valve closure reflecting the greater contribution by atrial contraction to late diastolic filling in these patients In patients with left ventricular hypertrophy and delayed mitral valve closure the VAW was normal reflecting lesser ventricular enlargement with atrial contraction than in the other patients with left ventricular hypertrophy This suggested a greater impairment to left ventricular filling in these patients Therefore, the VAW appears to be an indicator of abnormalities of late diastolic filling caused by left ventricular hypertrophy

We greatfully acknowledge the secretarial assistance of Ms Fern S Pobiner and Ms Mona Schacht

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Leukocyte function after aortic valve replacement

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Patients with aortic ball valve prostheses regularly develop intravascular hemolysis to a higher or lesser degree,[1] and their platelet reactivity is disturbed The shortened survival of red cells[3] and platelets[4 6] is most probably caused by direct mechanical trauma inflicted by the valve The prosthetic valve may also damage leukocytes and their functional capacity may be reduced, although sepsis is a rather rare cause of death in the late course of aortic valve replacement

The consumption of oxygen by leukocytes during phagocytosis reflects their functional capacity [7 9] The purpose of the present study was to evaluate leukocyte function with an oxygen consumption test in patients with aortic ball valve prostheses and compare the results with normal volunteers

Materials and methods

Thirty eight patients with prosthetic heart valves were included, 24 men and 14 women They had all Starr Edwards aortic ball valves implanted on average 4 5 years previously Two modifications of the valve had been used[10], 16 had the older type 1200 which inflicts less trauma upon red cells and platelets than does type 2300 [1] which had been implanted in 22 of the patients The mean age in the patient group was 54 years The normal material consisted of 50 healthy blood donors 42 men and eight women their mean age being 46 years

Blood was collected into siliconized glass tubes containing heparin, final concentration 0 007 M

Isolation of leukocytes was done according to Bøyum [11] A suspension rich in white cells and platelets was obtained

Leukocyte counting in the suspensions was done with an electronic particle counter (Celloscope 101, AB Lars Ljungberg & Co Stockholm Sweden) [12] Counting in citrated blood (nine parts of blood to one part of 3 1 per cent of sodium citrate) was done microscopically using a hemocytometer, and the numbers were corrected for dilution with citrate Differential leukocyte counting was also done microscopically after conventional staining of blood films

Oxygen consumption during phagocytosis was measured polarographically with a Clark oxygen electrode (Yellow Springs Instruments Co Yellow Springs Ohio U S A) at 37° C in 2 5 ml of leukocyte suspension during magnetic stirring [7 13] The electrode was connected to a Beckman 10 inch recorder (Beckman Instruments Inc Fullerton California U S A) When the endogenous oxygen consumption had reached a stable level 100 µl of a 10 per cent polystyrene latex particle suspension (Dow Chemical Company Midland Michigan, U S A) were added The oxygen consumption was then measured in nanoatoms per minute and calculated per 10^6 leukocytes [7]

Serum lactate dehydrogenase (LDH) was determined as described previously at 25° C and expressed in international units [14]

Results

The elevated serum LDH levels in the ball valve patients reflect the degree of intravascular hemolysis (Table I) which differed considerably between them The mean number of leukocytes

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Received for publication Nov 11 1977
Accepted for publication Jan 11 1978

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0002-8703/78/110624 + 03$00 30/0 © 1978 The C V Mosby Co

Table I Serum lactate dehydrogenase levels white cell counts and oxygen consumption during phagocytosis in patients with Starr Edwards aortic ball valve prostheses and in healthy subjects

	Patients with ball valves		*Healthy individuals*		*Student's t test*
	Mean	*SD*	*Mean*	*SD*	
Serum lactate dehydrogenase (U/L)	442 7	191 2	122.2	21 7	$p < 0.001$
Leucocytes per ml. of blood	7 16	1 96	7 33	1.34	N.S
Oxygen consumption (n atoms/min /10[6] leucocytes)	3 95	1 25	4 16	1.31	N.S

was not significantly higher in the healthy subjects Differential counting did not reveal marked differences but slightly more younger neutrophilic granulocytes were found in the patients The increase in oxygen consumption by leukocytes during phagocytosis was not significantly lower in the ball valve patients than in the healthy subjects The consumption by leukocytes from one ml of blood was calculated the mean values being 28 3 nano atoms in the patients and 30 5 in the normal material The difference was not statistically significant The individual values for oxygen consumption was compared with the degree of intravascular hemolysis but no significant correlation was found

Discussion

Phagocytosis is accompanied by an increase in oxygen consumption which can be quite accurately measured by the polarographic technique[7] The method allows examination of leukocytes that are not separated from plasma and it reflects the total phagocytic capacity of all leukocytes Thus the procedure mimics the in vivo situation as far as possible

The study did not disclose a significantly reduced oxygen consumption by leukocytes during phagocytosis in patients with prosthetic heart valves indicating that the functional capacity of the cells is rendered intact and their defense mechanisms against bacterial infections are not weakened Theoretically the leukocyte function could be disturbed by the trauma from the prosthetic valves or their capacity for phagocytosis could be reduced because they had engulfed circulating particles derived from other damaged cells Our results indicate however that leukocytes are not easily affected by mechanical trauma or that new cells are formed so rapidly that a normal total capacity for phagocytosis is maintained Possibly the polarographic method is not sensitive enough to disclose minor disturbances of leukocyte function

The results suggest that the cells are able to maintain phagocytosis even under more unfavorable conditions which may occur during severe bacterial infections with endotoxemia Thus leukocytosis has been found to develop in dogs shortly after endotoxin infusions in spite of intravascular coagulation and shock[15]

In conclusion the results indicate that the part of the defense against infections that depends upon leukocyte function is not weakened in patients with prosthetic heart valves

Summary

Leukocyte function was studied in patients with prosthetic heart valves by oxygen consumption measurements during phagocytosis of polystyrene latex particles The consumption reflects the phagocytotic capacity of the cells In 38 patients with Starr Edwards aortic ball valves the mean oxygen consumption was 3 95 nano atoms per minute per 10^6 leukocytes as compared to 4 15 in 50 healthy subjects the difference not being statistically significant The number of leukocytes per ml of blood and the distribution of cell types was quite similar in the two groups although slightly more younger cells were found in the patients It is concluded that the capacity for phagocytosis is not significantly reduced after aortic ball valve implantation

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Quinidine pharmacokinetics in patients with cirrhosis or receiving propranolol

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Quinidine is the prototype Class I antiarrhythmic agent and continues to find wide clinical usage It is metabolized by the liver to nonphenolic hydroxy derivatives and their congugates which are more water soluble than quinidine these metabolites are in turn excreted by the kidney [2] An active quinidine metabolite O desmethyl quinidine has been identified but its clinical significance has not been delineated [3]

Although the binding of quinidine to plasma proteins is decreased in patients with cirrhosis and one patient with cirrhosis and the hepatorenal syndrome had an abnormally prolonged quinidine half life [5] a systematic investigation of quinidine pharmacokinetics in patients with hepatic dysfunction has not been available

In the present study a single 200 mg oral dose of quinidine was administered to control patients patients with moderate to severe cirrhosis and patients receiving propranolol Quinidine concentration-time curves were constructed and the data were analyzed to answer the following specific questions

1 Does hepatic dysfunction or propranolol alter quinidine pharmacokinetics?

2 If there is an alteration how are half life and calculated volume of distribution and clearance individually altered?

3 Is the binding of quinidine to plasma proteins changed?

4 What are the relevant therapeutic implications of these findings?

Methods

Patients were selected from the *in patient* population of Temple University Health Sciences Center The study was explained in detail to each patient and signed consent was obtained from each participant The patients were divided into the following groups

Control group Eight patients with no evidence of impaired hepatic function hypoalbuminemia congestive heart failure or renal failure Their diagnoses were coronary artery disease with angina pectoris—five atypical chest pain with normal coronary arteries—two and mild mitral stenosis—one

Cirrhotic group Eight patients with a history of chronic alcohol abuse and physical evidence of cirrhosis (e g spider angiomata wasting ascites *and/or* hepatomegaly) and confirmatory laboratory tests were selected In each case the diagnosis of Laennec cirrhosis had been proven by percutaneous liver biopsy although in no case was the biopsy performed solely for the purposes of this study Patients with co existing renal failure or congestive heart failure were excluded from this group Additional diagnoses included anemia—five electrolyte imbalance—three urinary tract infection—one improving hepatic encephalopathy—two duodenal ulcer—one diabetes mellitus—one

Cholestatic group Two patients were incidentally studied one of whom had biliary cirrhosis

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Supported in part by Grant No RR05417 from the Division of Research Resources, National Institutes of Health This *research* was also assisted by a grant pursuant to Honorable Louis C Bechtle, Judge of the United States District Court for the Eastern District of Pennsylvania. We are pleased to make this acknowledgment and express our sincere gratitude for this aid.

Received for publication Nov 29 1977

Accepted for publication Feb 27 1978

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0002-8703/78/110677 + 09$00 90/0 © 1978 The C V Mosby Co

Table I Clinical profiles of patients studied

Patient group	Age	Sex	Total protein (Gm %)	Albumin (Gm %)	Bili rubin (mg %)	Alkaline phos phatase (IU)	SGOT (IU)	Blood urea nitrogen (mg %)	Creat inine (mg %)	Pro thrombin time (SEC)	Urinary pH
Control group (8)											
Mean ± S E	43 67	3F 5M	6 8 ± 2	4 2 ± 1	4 ± 1	70 ± 8	26 ± 5	15 ± 1	1 1 ± 1	11 ± 2	6 2 ± 1
Cirrhotic group (8)											
1 T B	45	M	6 4	2 2	3 0	150	30	11	0 9	13 9	7 0
2 W H	51	M	8 1	2 3	14 5	238	122	5	0 8	13 6	7 0
3 L K	54	F	6 8	1 6	4 1	138	54	13	1 2	17 8	5 0
4 M P	49	M	5 7	2 5	5 6	139	116	6	0 9	12 0	7 0
5 R F	46	M	8 5	3 2	8 2	105	65	17	0 9	11 8	6 5
6 H N	53	F	7 8	2 5	8 0	185	116	12	0 9	15 0	6 0
7 A L	47	F	7 0	2 8	5 8	229	103	7	0 8	12 6	6 0
8 L S	44	M	7 7	2 6	1 9	105	243	9	0 6	13 1	6 0
Mean ± S E	44 54	3F 5M	7 2 ± 3	2 5 ± 2§	6 4 ± 1 4‡	161 ± 18§	106 ± 23§	10 ± 1*	9 ± 1	14 ± 1 0‡	6 3 ± 2
Cholestatic group (2)											
1 T S	29	M	6 2	3 1	10 5	500	127	6	1 0	11 0	6 0
2 C S	37	M	7 6	3 4	4 4	1170	123	7	0 3	10 1	7 5
Propranolol group (7)											
Mean ± S E	47 56	3F 4M	6 5 ± 2	3 6 ± 1	4 ± 1	88 ± 13	49 ± 17	16 ± 3	1 1 ± 1	11 ± 3	6 3 ± 3

SGOT = serum glutamic oxalacetic transaminase
*p < 05 †p < 01 ‡p < 005 §p < 001 level of significance as compared to control group by unpaired Student s t test

and the other alcoholic liver disease characterized by fatty infiltration and bile plugging without fibrosis Neither patient had renal failure or congestive heart failure Additional diagnoses included alcohol withdrawal seizures and anemia—one

Propranolol group Seven patients receiving stable propranolol doses ranging from 40 to 400 mg per day were studied (40 mg per day—W M in Table II, 160 mg—R H , 240 mg—M C C G , S R , 320 mg ,—J C , 400 mg—E F) Patients with coexisting hypoalbuminemia, renal failure congestive heart failure, or liver disease were excluded from this group Their diagnoses were coronary artery disease—six stable angina pectoris—three, unstable angina—one hypertension—two, inferior myocardial infarction—one subendocardial myocardial infarction—one and idiopathic hypertrophic subaortic stenosis—one

Each patient was fully evaluated including a complete history (with particular note to alcohol intake, both recent and remote) physical examination, and a medication history (with emphasis on prior use of quinidine and known sensitivity to it) In addition, a complete blood count and differential, electrocardiogram serum glutamic oxalacetic transaminase alkaline phosphatase, lactate dehydrogenase, bilirubin prothrombin time urinary pH, total protein and albumin were obtained Each patient was screened for glucose 6 phosphate dehydrogenase deficiency No patient had evidence of malabsorption

Drug administration protocol Each patient received a 200 mg oral dose of quinidine sulfate before breakfast Patients were monitored for side effects throughout the day Blood samples were obtained at hourly intervals for four hours and subsequently at two hour intervals until 12 hours after the oral dose

Quinidine determinations Quinidine concentrations were determined by both a double extraction[6, 7] and a protein precipitate method[8] The double extraction method is more specific[9, 10] and has been shown to compare favorably with gas chromatographic and gas chromatographic/mass-spectrometric techniques[11] The protein precipitate method is less specific, measuring both quinidine and its water soluble metabolites Quinidine binding to plasma proteins was determined by an ultrafiltration method[12] using the double extraction assay method

Data analysis Quinidine concentration time

Table II Quinidine pharmacokinetic data

Group	*Half life (hours)*	*Volume of distribution (L/Kg)*	*Clearance (ml/min/Kg)*	*Peak level (μg/mL)*	*Time to peak level (hours)*	*Percent unbound*
Control group (8)						
1 TH	4 5	2 25	5 8	70	2	24.5
2 TF	5 5	2 15	4 5	83	4	33 5
3 IC	6	2 48	4 8	86	6	20
4 JG	9	2 43	3 1	82	4	10 5
5 IG	5 5	3 0?	6.3	69	3 5	39 5
6 WR	7	3 02	5 0	58	2 5	65
7 HT	4	2 33	6 8	94	1 5	15
8 RD	6	2 00	3 8	97	1	12
Mean ± S E	6 ± 5	2 5 ± 1	5 0 ± 4	.80 ± 05		
Cirrhotic group (8)						
1 TB	8	3 44	5 0	70	2	26 5
2 WH	9	5 15	6 6	57	1	47
3 LK.	9	3 66	4 7	83	1	50 5
4 MP	6 5	3 56	6 3	74	2	40 5
5 RF	9	1 93	2 4	1 13	1	14 7
6 HN	11	5 41	5 6	41	6	26
7 AL	12	3 76	3 6	94	3	31
8 LS	6	3 64	7 0	57	1	54 5
Mean ± S E	9 ± 1†	3 8 ± 4†	5 2 ± 6	74 ± 08		
Propranolol group (7)						
1 EF	4	–	–	–	–	22
2 JC	5	1 7	4 0	1 29	1	25
3 RH	7	2 4	3 9	.59	6	41
4 WM	5.5	1 6	3 4	1 63	1	36
5 MC	5	2 2	5 0	77	1	19
6 CG	7	2 8	1 7	1 4	1	13
7 SR	7 5	1 4	9	1 8	2 5	15
Mean ± S E	6 ± 5	2 0 ± .2	3 1 ± 6	1 25 ± 20		

SGOT = serum glutam c-o l cetic transaminase
p < 05 †p < .01 ‡p < 005 §p < 001 le l of sign fica ce as compared to co trol group by u p ired Student s t test

curves were plotted on semilogarithmic paper and the best straight line was fitted to the exponential disappearance phase of the curve Quinidine half life was thus determined Volume of distribution and clearance were calculated by the following formulas [3]

$$\text{Volume of distribution} = \frac{D \quad T1/2}{0.693\,AUC}$$

$$\text{Clearance} = \frac{D}{AUC}$$

where *D* represents milligrams of quinidine base available to the circulation (85 per cent of the 200 mg oral quinidine sulfate dose) *T1/2* is the half life in hours determined as above and *AUC* is the area under the concentration time curve in mg h/ml (calculated to infinity) Clearance and volume of distribution were adjusted per kilo gram of body weight

Statistics Mean and standard error were calculated for each of the parameters and the unpaired Student s t test was used to calculate statistical significance [15]

Results

Patient profiles (Table I) The age range male to female ratio and random urinary pH were not different between control cirrhotic and propran olol groups All patients had creatinine concen trations which fell within the normal range Routine laboratory data and liver function tests fell within the normal range for each patient within the control and propanolol groups The cirrhotic group had significantly lower albumin and blood urea nitrogen concentrations and significantly higher bilirubin serum glutamic oxalacetic transaminase activity alkaline phos phatase and prothrombin time than the control group The two patients with cholestatic liver disease were both males and were younger than the other patients studied They had normal

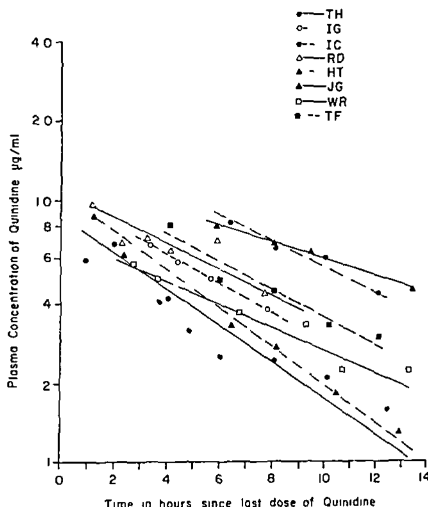


Fig 1 Plasma quinidine concentrations measured by the double extraction method during the logarithmic disappearance phase of the concentration-time curve in eight control patients

prothrombin times albumin levels greater than 3 mg per cent and markedly elevated alkaline phosphatase values

Quinidine pharmacokinetics (Table II Figs 1 through 4) The half life of quinidine was significantly prolonged (9 ± 1hr) in the cirrhotic group when compared to the control group (6 ± 0 5 hr, p < 01, Fig 4) Six of the eight patients in the cirrhotic group had quinidine half lives of 8 hours or greater (i e, greater than the mean plus two standard errors), whereas only one of the control group had a half life that long In contrast to the significantly prolonged half life of quinidine in patients with cirrhosis, the quinidine clearance value in the cirrhotic patients (5 2 ± 6 ml / min /Kg) was almost identical to that of the control group (5 0 ± 4 ml /min /Kg) The prolongation of half life was related to a significantly greater volume of distribution of quinidine in the cirrhotic group (3 8 ± 4 L /Kg) when compared to the control group (2 5 ± 1 L /Kg, p < 01) This increase in volume of distribution did not significantly correlate to serum albumin (R = – 39) bilirubin (R = 42) or prothrombin time (R = 37)

The half life of quinidine in the propranolol group was normal (6 ± 5 hr), however, the clearance rate (3 1 ± 6 ml /min /Kg) was significantly reduced when compared to the control group (p < 05) Clearance rates did not correlate to propranolol dose (r = 05) A decreased volume of distribution was evident in some of the propranolol patients and was further implied by their higher peak levels (1 25 ± 2 µg/ml vs 80 ± 5 µg/ml in the control group, p < 05)

The two patients with cholestatic liver disease had short half lives (4 and 2 5 hr) normal volumes of distribution and clearance rates higher (7 3 and 10 7 ml /min /Kg) than any of the other patients studied

Quinidine binding to plasma proteins was determined in each of the patients and a greater than 25 per cent unbound fraction was considered abnormal[4] Abnormal binding was identified in three of the eight control patients two of the five propranolol patients seven of the eight patients

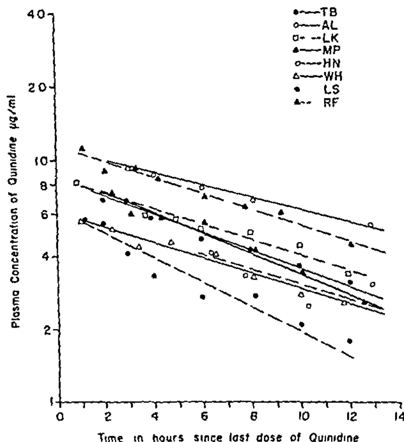


Fig 2 Plasma quinidine concentrations measured by the double-extraction method during the logarithmic disappearance phase of the concentration-time curve in eight patients with cirrhosis

with cirrhosis and both of the patients with cholestatic liver disease Although as a group the cirrhotic patients had impaired quinidine binding and low serum albumen concentrations the per cent unbound quinidine did not significantly correlate with serum albumen bilirubin or the prothrombin time

The ratio of the quinidine concentration determined by the protein precipitate method to the quinidine concentration determined by the double extraction method may be used as an index of the relative concentration of circulating quinidine metabolites[1] This ratio was determined in our main three groups of patients at 1 hour after their peak quinidine concentration and at 10 hours after the dose was given In the control group this ratio was 1 5 ± 1 at one hour after the peak and 1.5 ± 1 at 10 hours after the dose In the propranolol group the ratio was very similar (1.5 ± 1 one hour after the peak and 1 6 ± 1 at 10 hours after the dose) In the cirrhotic group however the ratio one hour after the peak was significantly lower (1 0 ± 1, p < 01) than in the control group By ten hours after the dose this ratio (1 2 ± 2) was still lower although the difference was not statistically significant

Absorption Peak levels were obtained within 2 5 hours after the dose of quinidine in 16 of 25 patients Variability was noted three patients (one of each of the major groups) showing delayed peaks at 6 hours after the dose

Side effects and toxicity No major side effects were noted Two patients had gastrointestinal side effects—one had nausea and the other nausea and diarrhea

Discussion

This study characterizes the pharmacokinetics of quinidine in patients with liver dysfunction and receiving propranolol Despite the knowledge that quinidine is metabolized by first order kinetics in the liver little information is available on the effect of liver dysfunction on quinidine pharmacokinetics In a single patient with both alco

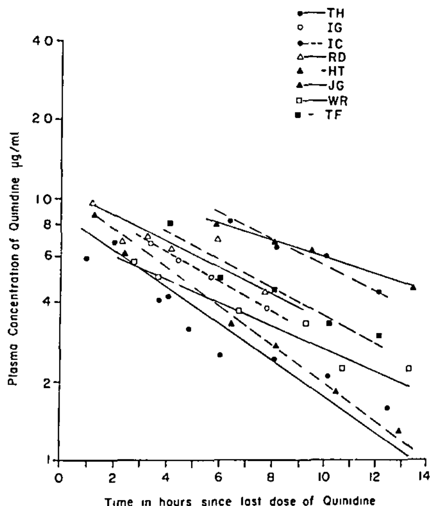


Fig 1 Plasma quinidine concentrations measured by the double extraction method during the logarithmic disappearance phase of the concentration-time curve in eight control patients

prothrombin times, albumin levels greater than 3 mg per cent and markedly elevated alkaline phosphatase values

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Quinidine binding to plasma proteins was determined in each of the patients and a greater than 25 per cent unbound fraction was considered abnormal[4] Abnormal binding was identified in three of the eight control patients two of the five propranolol patients seven of the eight patients

binding of quinidine to plasma proteins of patients with renal insufficiency is normal[17] Thus changes in renal function and urinary pH have little consequence on quinidine therapeutics in the usual patient

In the present study the effects of hepatic dysfunction and propranolol on quinidine pharmacokinetics was studied in detail Four major parameters play a role in hepatic biotransformation first the hepatic blood flow representing that portion of the cardiac output which transverses the liver second the effects of anatomic disarray of the hepatic circulation causing shunting third the binding of drug to serum and hepatic sites and last the activity of the enzymes metabolizing that drug[19] Cirrhosis may interfere with any or all of the latter three parameters Propranolol is known to reduce hepatic blood flow[9] and can interfere with the metabolism of highly cleared drugs e g. lidocaine and propranolol[20] Since patients with arrhythmias may have hepatic dysfunction (and vice versa) and since patients with cardiac disease may receive both quinidine and propranolol simultaneously these interrelationships have obvious clinical importance

In our current study the pharmackinetics of quinidine were assessed after an oral dose Using this method serum half life can be directly determined however both clearance and volume of distribution are calculated values and are dependent on knowing how much drug reaches the circulation The amount of quinidine reaching the circulation is in turn dependent on completeness of absorption and the hepatic first pass effect Data regarding these parameters is scant however quinidine availability after the administration of quinidine sulfate to nine cardiac patients was 87 ± 7 per cent and to eleven healthy volunteers was 81 9 ± 3 4 per cent Therefore in the sulfate form quinidine is about 85 per cent available to the circulation and had a tolerable inter patient variability The gluconate form has 47 to 99 per cent (mean 73 per cent) and 69 1 ± 2 8 per cent availability of quinidine and was specifically avoided Although pharmacokinetics could have been more precisely measured the intravenous use of quinidine was also specifically avoided because many of our patients were clinically ill and the increased risks of this route of administration were not justified

Our control group had a mean quinidine half life (6 ± 5 hr) volume of distribution (2.5 ± 1 L/Kg) and clearance (5 0 ± 4 ml/min/Kg) comparable to those reported by other investigators[22] In contrast the cirrhotic group had a significantly prolonged quinidine half life (9 ± 1 hr) This prolonged half life was related not to an altered clearance rate of quinidine as might have been expected by their advanced degree of parenchymal liver destruction but rather to a significantly increased volume of distribution of quinidine This increase in volume of distribution is at least in part related to the decreased quinidine plasma protein binding found in patients with cirrhosis This pattern of prolonged half life and increased volume of distribution of a drug in cirrhosis was also found to be true for another antiarrhythmic base—lidocaine[23, 24] Furthermore the ratio of the quinidine level by the precipitate to the double extraction method gives an estimate of the amount of quinidine metabolites circulating at any given time[7] This ratio was significantly lower in the cirrhotic group when compared to the control group signifying fewer circulating metabolites in the cirrhotic patients this finding confirms the slowed production of metabolites in patients with cirrhosis

The two patients with cholestatic liver disease had normal volume of distribution accelerated clearances and shortened half lives These patients were significantly younger than the patients in the other groups Quinidine pharmacokinetics have been shown to be age related however the half life (4 and 2 5 hr) and clearance values (7 3 and 10 7 ml/min/Kg) of our two patients with cholestatic liver disease appear abnormal even when compared to the 12 healthy volunteers ages 23 to 31 years (half life 7 1 ± 0 7 hr and clearance 4 03 ± 0 35 ml/min/Kg) studied by Ochs and associates[25] Age did not vary significantly in the control cirrhotic or propranolol groups and should not be considered a variable in the assessment of their data The number of patients with cholestatic liver disease does not allow for generalization of these findings but does provide a basis for further investigation of such an effect and its as yet unknown mechanism

In contrast to the patients with liver disease patients receiving propranolol had normal quinidine half lives (6 ± 5 hr) but a significantly decreased rate of quinidine clearance Consistent with the normal quinidine half life accompanied by a decreased clearance rate was the tendency of these patients to have a decreased volume of

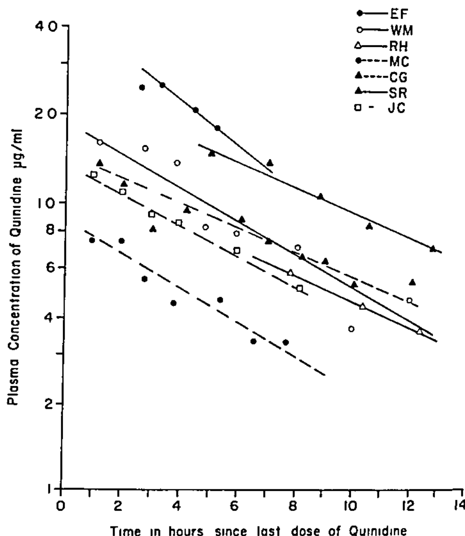


Fig 3 Plasma quinidine concentration measured by the double extraction method during the logarithmic disappearance phase of the concentration-time curve in seven patients receiving propranolol

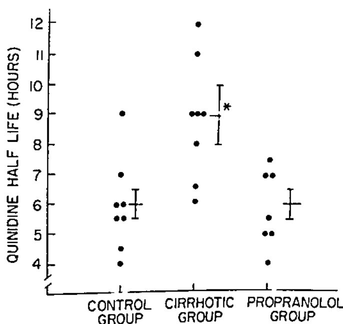


Fig 4 Quinidine half lives in control cirrhotic and propranolol patient groups *The horizontal and vertical lines* indicate mean and standard error of the mean respectively The * indicates a significant (p < 01) prolongation of half life in the cirrhotic group when compared with that in the control group (Student s t test unpaired)

hol related liver disease and the hepato renal syndrome a prolonged quinidine half life and an increased volume of distribution were found[3] However, this example is complicated by the obscure pathophysiology of the hepato renal syndrome Quinidine binding to plasma proteins has been shown to be decreased in many patients with cirrhosis[4] However, such binding information must be combined with half life data and calculated clearance and volume of distribution values to allow fully meaningful therapeutic recommendations

Although the liver serves as the major organ of quinidine biotransformation quinidine elimination had been ascribed to renal excretion[14] In 1969, Gerhardt and associates[17] found that quinidine excretion is enhanced in acidic urine however only 20 per cent of the total quinidine dose was excreted unchanged even in patients with aciduria Normal quinidine half life has been confirmed in patients with poor renal function[7] and in three anephric patients[18] Furthermore the

cantly reduced quinidine clearance (3 3 ± 7 ml/min/Kg vs. 5 3 ± 5 ml/min/Kg in controls p < 05) and higher peak concentrations (1.25 ± .20 µg/ml vs 80 ± 5 µg/ml in controls p < 05)

Therefore in patients receiving propranolol quinidine levels may be higher than expected shortly after dosage and therefore a potential for transient toxicity exists in these patients Maintenance quinidine dosage may have to be reduced in patients with moderate to severe hepatic cirrhosis but not in patients receiving propranolol Total quinidine concentration measurement underestimate free quinidine concentrations in most cirrhotic patients

We wish to thank Ms Robin Leech for her expert technical assistance and Marcus M Reidenberg M D for his continued encouragement and for his review of the final manuscript.

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distribution and significantly higher peak concentrations of quinidine Propranolol may cause this effect by a decrease in hepatic blood flow, changing intrinsic hepatic clearance, or altering absorption Since quinidine is not a highly extracted drug propranolol mediated alterations in hepatic flow should be insufficient, in and of itself, to cause the marked reduced in clearance we observed (control group 5 0 ± 4 ml /min /Kg vs propranolol group 3 1 ± 6 ml /min /Kg) Propranolol has metabolic effects, but to date these are best described only as they relate to its anti adrenergic properties [26] There is no evidence for an effect of propranolol on quinidine absorption per se and thus the mechanism of this interaction remains unclear Again, because clearance and volume of distribution data are derived numbers more emphasis can be placed on the normal quinidine half life and higher peak levels immediately after dosage

Abnormalities in the binding of quinidine to plasma proteins were found infrequently in the control and propranolol group but commonly in the cirrhotic (seven of eight patients) and obstructive (two of two patients) groups This frequency of quinidine binding abnormalities is consistant with the previous findings of Affrime and Reidenberg [4]

Therapeutically quinidine is usually administered using a cautious test dose In cirrhotic patients the increased volume of quinidine distribution which would in itself cause a lower than predicted quinidine concentration is opposed by the decrease in quinidine binding to plasma proteins The over all effect is an unpredictable free (active) quinidine concentration In patients receiving propranolol, the decrease in clearance and tendency to lower volumes of distribution can result in higher than predicted plasma quinidine concentrations especially soon after a quinidine dose Because of the small amount (100 to 200 mg) of quinidine usually used, the administration of a standard test dose should not be a problem in either patients with cirrhosis or those receiving propranolol Initiating quinidine therapy with a larger loading dose (e g 600 mg) as has been recently advocated[27] should be done with extreme caution, if at all in patients with hepatic dysfunction or receiving propranolol

During maintenance quinidine therapy drug dosage may need to be reduced or administered at greater inter dose intervals because of an over all 50 per cent prolongation of quinidine half life in cirrhotic patients Furthermore, quinidine concentration determinations may underestimate free drug concentrations in cirrhotic patients because of decreased binding to plasma proteins, thus in the face of cirrhosis the lower end of the therapeutic range of 2 3 to 5 µg/ml [1] should be used

Standard maintenance quinidine therapy should be acceptable for the majority of patients receiving propranolol However the tendency to higher peak plasma levels might lead to toxic manifestations shortly after a dose Decreasing the dose size and increasing dose frequency while maintaining the same total daily dose might be helpful under such circumstances

In conclusion, quinidine pharmacokinetics are altered in patients with hepatic cirrhosis and in patients receiving propranolol Patients with moderate to severe cirrhosis had a moderately prolonged quinidine half life accompanied by evidence for normal absorption, an increased volume of distribution (coincident with impaired binding of quinidine to plasma proteins) and a normal clearance rate In contrast, patients receiving propranolol had a normal quinidine half life accompanied by evidence for normal absorption, a decreased clearance rate and higher peak levels Analysis of these alterations has lead to the specific therapeutic recommendations enumerated above

Summary

Quinidine pharmacokinetics (half life volume of distribution and clearance) as well as protein binding were evaluated following a single 200 mg oral dose of quinidine sulfate in eight control patients in eight patients with moderate to severe cirrhosis and in seven patients receiving 40 to 400 mg /day of propranolol Patients with cirrhosis had a significantly longer quinidine half life (9 ± 1 hr p < 01) when compared to control patients (6 ± 0 5h) This was not related to a reduced quinidine clearance rate but rather to an increase in quinidine volume of distribution (4 1 ± 4 L /Kg in cirrhotic patients vs 2 6 ± 1 L /Kg in control patients, p < 01) Abnormal quinidine binding (greater than 25 per cent unbound fraction) was noted in seven of the eight cirrhotic patients In contrast patients receiving propranolol had a normal quinidine half life of 6 ± 0 5 hr However these patients had a signifi

degree left anterior oblique position The left ventricular (LV) and right ventricular (RV) dimensions were recorded with the echobeam in a standard plane to guard against forshortening of the measured diameter of the LV (minor axis) The transducer was positioned in the third to fifth interspace along the left sternal border and directed posteriorly to define the endocardial surfaces of the interventricular septum (IVS) and LV posterior wall (LVPW) at the level of the tips of the mitral leaflets The interspace selected was that in which the mitral valve could be recorded with the transducer perpendicular to the chest wall[5] The echo beam was then directed to record the other intracardiac structures and chambers[6]

The time intervals of the cardiac cycle[7,8] were recorded with an Electronics for Medicine VR 6 photographic recorder using a piezoelectric crystal transducer A simultaneous electrocardiogram (ECG) phonocardiogram (PCG) and apexcardiogram (ACG) or carotid pulse tracing were recorded and these were superimposed on the echocardiographic recording of the LV The mean measurements over several respiratory cycles were used in the analysis of both the echocardiogram and the systolic time interval recordings

Data analysis

Echocardiography The *left ventricular dimension* (minor diameter) was measured at end diastole (Dd) and at end systole (Ds) (Fig 1) The *percentage shortening* of the LV diameter during systole (%ΔS) was calculated where

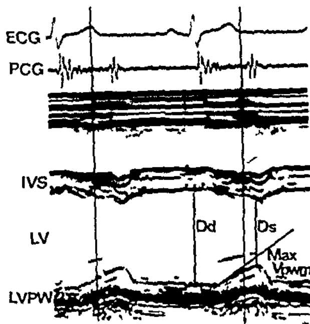
$$\%\Delta S = \frac{Dd - Ds}{Dd} \times 100\%$$

For comparison with other measurements in the literature we also calculated stroke index (SI) and cardiac index (CI) LV volumes were calculated from the cube of the diameter measurements echocardiographic SI was the difference between EDV and ESV (indexed for body surface area) and CI was calculated by multiplying SI by heart rate (HR)

The following measurements were made of the velocity of LV contraction

a. *The mean velocity of circumferential fibre shortening* (mean Vcf) was calculated[9] where

$$\text{mean Vcf} = \frac{\%\Delta S}{LVET} \times 100 \text{ (circ/sec)}$$



1 Electrocardiogram *(ECG)* phonocardiogram *(PCG)* and echocardiogram to show method for measuring left ventricular (LV) dimensions The internal LV diameter is measured at end-diastole *(Dd)* and end systole *(Ds)* Maximum velocity of posterior LV wall motion *(Max Vpwm)* is measured as the steepest tangent to the movement of the posterior LV endocardial surface *The solid vertical time lines* are 1 second markers. *IVS* = interventricular septum *LVPW* = left ventricular posterior wall

LVET is the left ventricular ejection time measured from the carotid pulse tracing

b *Maximum velocity of posterior wall motion* (max Vpwm) was the steepest tangent to the endocardial surface of the posterior LV wall during systole (Fig 1) The thickness of the posterior wall of the LV and the interventicular septum (IVS) were measured at end-diastole LV wall mass was calculated from the LV posterior wall thickness measurement and from LV Dd

The internal dimension of the *right ventricle* (RVID) was measured through the R wave of the QRS complex of the ECG *Aortic root* diameter was measured at end ventricular diastole The *left atrial* (LA) dimension was measured at end ventricular systole

The diastolic closure rate (EF slope) of the *anterior mitral leaflet* (AML) was measured The EF slope was essentially monophasic when recorded at a paper speed of 50 mm/sec so that there was no ambiguity in measurement[1] The mitral EF slope is related to early diastolic compliance of the LV in the absence of mitral valve disease[12] The total amplitude of movement

Left ventricular function in β-thalassemia and the effect of multiple transfusions

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Cardiac failure is a common and life threatening complication of the severe forms of the thalassemia syndrome [1,2] The patients suffer from severe chronic anemia from infancy due to ineffective erythropoiesis and increased hemolysis and require repeated blood transfusions they develop severe progressive iron overload which may lead to severe congestive cardiac failure, arrhythmias and death in the second decade The clinical spectrum of thalassemia is well described but there are no detailed studies of cardiac or left ventricular (LV) function This information is of importance in the evaluation of different therapeutic measures e g, hypertransfusion as compared to moderate transfusion regimens and the effects of long term therapy with iron chelators

We have studied a group of patients with β thalassemia major and intermedia by non invasive techniques—echocardiography and systolic time interval measurements—to examine the effects of chronic severe anemia and the effects of multiple transfusions on cardiac chamber size and on LV function

Patients

A consecutive group of 23 patients with thalassemia was studied All the patients were homozygous for β thalassemia Their detailed hematological and hemoglobin analyses have been reported in previous communications [3,4] Twenty of them were splenectomized They were divided into three groups on the basis of their transfusion requirements (Table I)

Group 1 consisted of seven patients who did not require blood transfusion or who had received a total of less than 10 transfusions on the basis of their milder clinical course They were classified as having thalassemia intermedia' Their ages ranged from 11 to 29 years (mean 19 ± 6 years)

Group 2 (five patients) had β thalassemia major with a moderate course These patients had received 10 to 80 blood transfusions Their ages ranged from 14 to 23 years

Group 3 (11 patients) had β thalassemia major and were more ill They were heavily transfused and had received a total of more than 80 blood transfusions six patients received more than 100 transfusions and one more than 200 transfusions Patients in this group were younger (age range 7 to 22 years) ($p = 0.05$) and had a smaller body surface area ($p < 0.001$)

Methods

Data acquisition All patients were examined clinically and the detailed cardiac studies were made after the maximum time interval between transfusions Echocardiograms were recorded with an Ekoline 20A echocardiograph (Smith Kline Instruments) coupled to a VR 6 Electronics for Medicine photographic strip chart recorder A 2 25 MHz transducer was used and this was focused at 7 5 cm Recordings were made with the patient in a semisupine anteroposterior or a 20

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Received for publication Dec 2 1977

Accepted for publication Apr 25 1978

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Table II Echocardiographic measurements

Patient	BSA (M)	Dd* (cm)	Dd/BSA (cm /M)	Ds (cm)	%ΔS	SI (ml /M)	CI (L /min./ M)	LVPW (cm)	IVS (cm)	LV wall mass (g /M)	Max Vpum (mm./ sec)	Mean Vcf (circ / sec)
Group 1 Thalassemia intermedia												
1	11	51	44	32	37	84	76	08	09	154	60	1.32
2	160	60	38	40	35	95	76	08	19	146	61	111
3	1 0	45	26	25	44	46	38	1.2	11	146	58	147
4	1.20	4.3	36	2?	49	57	57	05	06	61	91	181
5	172	53	31	37	30	58	39	06	09	76	80	094
6	180	60	33	38	36	90	55	08	1.3	130	58	110
7	169	59	3.5	33	44	99	7?	08	08	136	63	148
Mean±1 SD	1.55±0.24	53±07	35±05	3?±06	39±6	76±20	59±15	08±02	11±04	121±34	67±12	1.?2±0.27
Group 2 Thalassemia major (moderate course)												
8	1.54	5.5	36	3.2	42	87	65	09	17	152	56	1.56
9	1.27	53	42	3.3	38	89	73	06	14	104	?6	141
10	118	52	44	34	35	85	83	06	07	109	84	1.25
11	125	56	45	35	38	106	93	05	09	94	50	131
12	1 6	48	35	30	38	61	45	04	11	51	6?	108
Mean±1 SD	13?±012	53±03	40±04	33±02	38±2	86±10	7.3±18	06±02	12±04	102±3?	66±13	132±016
Group 3 Thalassemia major (severe course)												
13	134	49	36	29	41	70	73	08	10	1?2	46	157
14	116	51	44	30	42	8?	59	07	–	136	57	129
15	115	46	40	–	–	–	–	11	10	212	77	–
16	140	60	43	43	29	97	94	11	08	?51	55	1.21
17	114	45	39	33	?7	5?	52	06	08	193	71	104
18	1?2	5.5	45	34	38	104	101	06	12	116	69	158
19	0 4	48	65	34	30	95	95	11	04	331	57	10?
20	1?4	49	40	31	37	71	74	05	07	74	75	–
21	104	52	50	25	53	120	106	05	–	99	73	184
22	114	46	40	?5	45	?3	71	08	06	128	54	166
23	1?5	56	45	33	41	11?	99	06	–	1?0	?6	154
Mean±1 SD	117±016	51+05	44±07	32±05	38±8	88±20	82±18	08±02	0.8±02	167±72	65±10	142±026
Normal values[6, 19, 30]		44±0.3	26 (193?)	28±03	36±4	36±7	25±06	09±01	09±01	92±17	53±9	1.2?±013

See text fo deta ls f bbreviat ns and ind es

PEP and LVET Δ Q A is the rate corrected value [6]

Isovolumic relaxation period (IRP) was measured as the time interval from aortic valve closure (A_2 on the PCG) to the onset of mitral valve opening (D point on the echocardiogram of the anterior mitral leaflet)

Critique of methods Echocardiographic measurements of LV function are widely used but the data must be analysed critically The single plane echocadiogram measures the minor diameter of the left ventricle in normal patients the LV is symmetrical and the echo measurements represent over all LV size and function but this is not necessarily so in patients with cardiac disease and ventricular dilatation [8] Nonetheless stroke volume and cardiac output were calculated for comparison with measurements in the literature

Statistical analysis Statistical analysis between the groups was made using Student s t test for unpaired data

Results

Clinical findings The present group of patients were not hypertransfused and their pretransfusion hemoglobin level was in the range of 7 to 10 g/100 ml The hemoglobin level was not signifi

Table I The patients

Patient	Age (years)	Sex	Approximate total no of transfusions	Hb (g /100 ml)	Splenectomy	Increased jugular venous pressure (cm)	Additional heart sounds S	Additional heart sounds S
Group 1 Thalassemia intermedia								
1	11	M	–	7 4	+	+2	+	–
2	23	F	7	7 9	+	+3	+	–
3	29	F	–	9 0	+	+2	+	–
4	12	F	–	8 6	+	+5	+	+
5	19	M	–	10 1	+	0	+	+
6	18	M	–	8 5	–	+5	–	+
7	20	M	–	9 5	–	0	+	–
Mean ± 1SD	19 ± 6			8 7 ± 0 9				
Group 2 Thalassemia major (moderate course)								
8	19	M	40	8 2	+	+4	++	–
9	16	M	60	9 3	+	+3	+	–
10	14	M	70	8 0	+	+3	++	–
11	23	F	55	7 4	+	0	+	–
12	20	F	58	8 7	+	0	+	–
Mean ± 1SD	18 ± 3			8 3 ± 0 6				
Group 3 Thalassemia major (severe course)								
13	17	F	137	7 3	+	+3	+	–
14	14	M	210	10 3	+	+2	+	–
15	17	M	155	7 2	+	+6	++	–
16	22	F	165	7 8	+	+4	+	–
17	16	M	180	9 4	+	+3	–	–
18	11	F	100	7 6	–	+4	+	–
19	7	M	85	9 4	+	+5	++	+
20	14	M	80	5 9	+	+2	+	+
21	12	M	90	8 6	+	+4	++	–
22	13	M	84	7 9	+	+3	+	+
23	14	F	110	7 8	+	+2	–	–
Mean ± 1SD	14 ± 4			8 1 ± 1 2				

of the AML (CE amplitude) was also measured The time from the peak of the A wave to closure (point C) was measured (AC time) Since the AC time is partly determined by the PR interval of the ECG, the time PR – AC was calculated A short PR – AC (i e prolonged AC) time is present in some patients with a high LV end diastolic pressure [13]

Time interval measurements

Pre ejection period (PEP) is the time interval from the onset of the QRS complex of the ECG till aortic valve opening, which corresponds to the upstroke of the carotid pulse tracing after correction for pulse transmission time delay *Isovolumic contraction time* (ICT) was measured from the onset of the upstroke of the apex cardiogram (U_{ACO}) to the moment of aortic valve opening [14]

$$ICT = PEP - (Q_{FCO} - U_{ACO})\text{msec}$$

PEP and *ICT* are related to velocity measurements of LV contractility but also depend on preload and afterload [15]

Left ventricular ejection time (LVET) was measured from the upstroke of the carotid pulse tracing to the nadir of the incisura of the dicrotic notch LVET depends on stroke volume afterload and myocardial contractility Since both PEP and LVET are heart rate dependent, we calculated Δ PEP and Δ LVET according to the method of Weissler and associates[16] where the Δ value is the difference between the measured time interval and the predicted normal time interval measurement at a given heart rate

The ratio *PEP/LVET* was calculated The measurement is less dependent on heart rate magnifies abnormalities of ventricular contractility, and is related to LV ejection fraction [17] Total electromechanical systole (Q A,) was the sum of

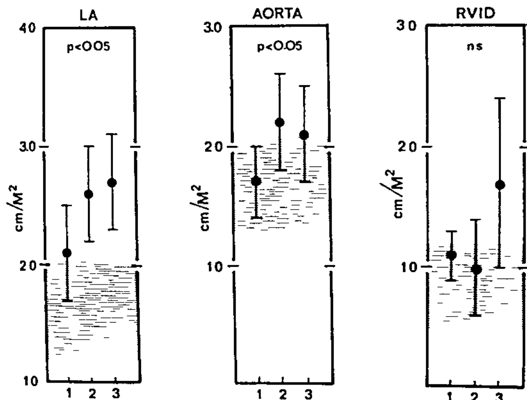


Fig 3 Left atrial diameter *(LA)* aortic root diameter and right ventricular internal diameter *(RVID)* in patients with thalassemia The LA aorta and right ventricle are enlarged in all three groups of patients and more so in Group 3 *(normal range shaded)* (p values compare Groups 1 and 3)

(Fig 4) The PR – AC time was less than 60 msec in one patient in Group 2 and in two patients in Group 3 This abnormality probably reflects an increase in LV end diastolic pressure in these patients but there was not a significant difference in the mean PR – AC time between the three groups (Fig 4)

Time interval measurements The time interval measurements are summarized in Table III and Fig 5 These measurements were in keeping with echocardiographic data and indicated good or increased LV performance in systole ΔPEP was decreased in all three groups of patients Δ LVET was prolonged and the PEP/LVET ratio was normal or decreased the changes were smaller in Group 3 ICT was normal or decreased Δ Q A_2 was slightly increased There was not a significant difference in the systolic time interval data between the three groups of patients

IRP was decreased in all three groups of patients The decreased IRP may indicate an increased left atrial pressure due to an alteration in LV compliance It may also be related to the short ICT or the low aortic closing pressure in patients with a hyperdynamic circulation and reduced diastolic blood pressure

Discussion

In thalassemia major and intermedia the heart is affected in two ways all the patients suffer from severe chronic anemia while those who require repeated blood transfusions develop additional iron overload Cardiac failure is a common clinical problem and is the major cause of death in the second decade of life [2]

Our study shows that all the cardiac chambers are enlarged in patients with *chronic anemia* due to thalassemia The LV is dilated and hypertrophied Systolic left ventricular function is apparently normal there is an increase in the velocity measurements of LV contraction (mean Vcf and max Vpwm) and in fractional fiber shortening (per cent ΔS) Stroke volume and cardiac output are high Systolic time interval measurements

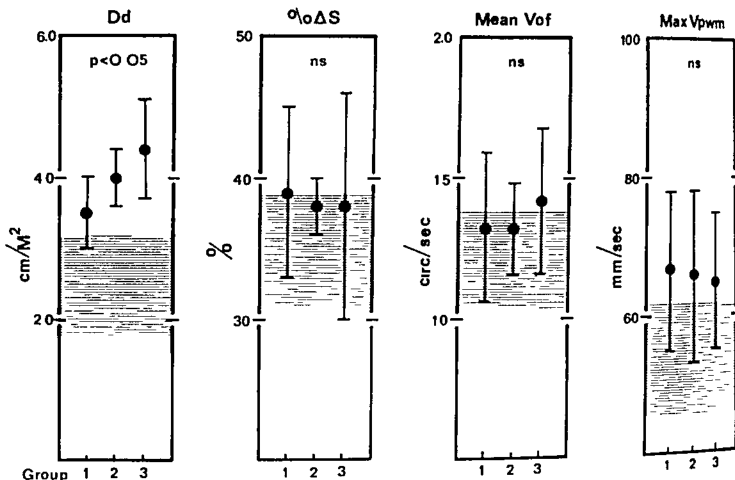


Fig 2 LV end diastolic dimension *(Dd)* percentage shortening during sytole (%ΔS) mean velocity of circumferential fiber shortening *(Vcf)* and maximum velocity of posterior wall motion *(Vpwm)* in patients with thalassemia Dd is increased in all three groups of patients and is larger in Group 3 ($p < 0.05$) Per cent ΔS mean Vcf and max Vpwm are normal or increased in all three groups *The shaded area* shows the normal range of values

cantly different in the three groups of patients (Table I) Five of the seven patients in Group 1 and three of the five in Group 2 had an increased jugular venous pressure and were in congestive heart failure at the time of study The jugular venous pressure was increased in all patients in Group 3 Most of the patients had a loud additional third heart sound and in several patients a fourth heart sound was also present These signs were more marked in patients in Group 3 even though these were younger patients One patient (Case 15) died in congestive heart failure three months after the study another patient (Case 20) developed bronze diabetes following repeated blood transfusions

Echocardiographic studies The *left ventricle* was enlarged Dd was greatly increased and was larger in patients who had than in those who had not received blood transfusions ($p < 0.05$) (Table II, Fig 2) Per cent ΔS was normal or increased Mean Vcf and max Vpwm were normal or increased, there was no statistical difference between the three groups of patients (Fig 2 Table II) Calculated stroke index and cardiac index were high and the increase in cardiac index was greatest in patients in Group 3 ($p < 0.001$) partly due to a greater increase in heart rate in these patients ($p < 0.05$) LV posterior wall thickness (LVPW) and interventricular septal thickness (IVS) were normal or increased LV wall mass tended to be greater in patients in Group 3 but the difference between Groups 1 and 3 was not significant statistically (Table II)

The *right ventricle* dimension (RVID) *left atrial* diameter, and *aortic root* diameter were increased and the increase in relation to the surface area was greater in patients in Group 3 (Fig 3)

The amplitude of motion of the anterior *mitral leaflet* (CE) was increased in Groups 1 and 2 but less so in Group 3 ($p < 0.05$) The mitral diastolic closure rate (EF slope) was normal or increased

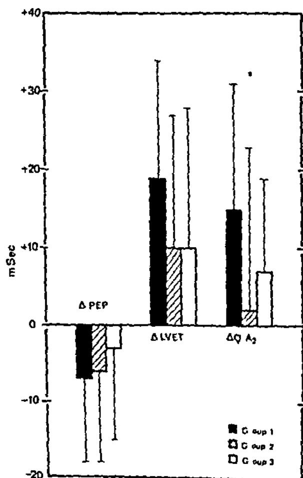


Fig 5 Systolic time interval measurements in the three groups of patients (*mean* ± 1 SD) expressed as the deviation from the normal rate-corrected value ΔPEP is decreased ΔLVET increased and ΔQ A increased The changes are greater in Group 1 but the differences are not statistically significant

cardiac decompensation only occuring when there is additional underlying primary cardiac disease [2]

Our results question the magnitude of the problem of *multiple transfusions* in the management of patients with thalassemia major Although these patients are more ill clinically at a younger age than patients in Groups 1 and 2 and are in "congestive cardiac failure with a high jugular venous pressure the previous assumption that there is poor systolic LV function with the hemodynamic picture of severe congestive cardiomyopathy at this stage of the disease seems to be incorrect [5] Although patients who receive multiple transfusions have larger hearts and *persistent* tachycardia stroke index is high and the cardiac index increased LV systolic function was normal in *all patients* in the group even in the patient who died in severe congestive heart failure within 3 months of the non invasive study We did not have the opportunity to perform echocardiography at the time of the terminal episode it is possible that serial echocardiographic studies may reveal terminal deterioration of LV performance in thalassemic patients dying of cardiac failure [24] *Nonetheless* systolic function of the LV is preserved until very late in the course of the disease despite the fact that histological studies show extensive iron deposition and myocardial damage in thalassemic patients who receive multiple transfusions [2] It *could* be argued that the presence of greater tachycardia and a larger heart without a further increase in systolic function (as compared to *patients in* Groups 1 and 2)

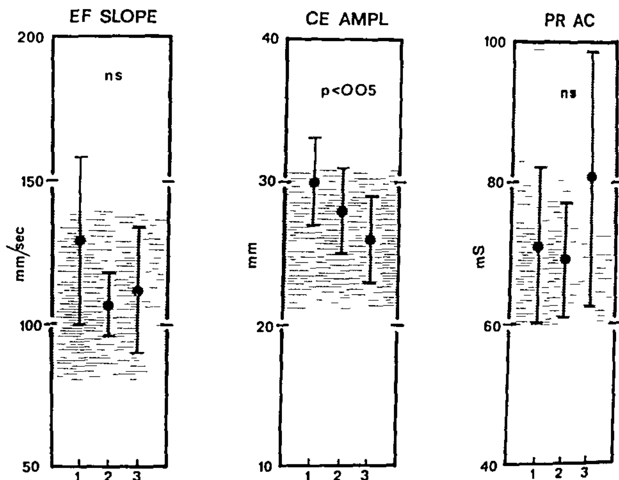


Fig 4 Diastolic closure rate *(EF slope)* amplitude of excursion *(CE)* and closure time *(PR – AC)* of the anterior mitral leaflet EF slope and CE amplitude are normal or increased but less so in Group 3 The mean PR – AC time is normal in all three groups

Table III Systolic time interval data

	ΔPEP (msec)	*ΔLVET* (msec)*	*PEP/LVET*	*ΔQ A (msec)*	*ICT (msec)*	*IRP (msec)*	*HR (beats/min)*
Group 1	–7 ± 11	+19 ± 15	0 30 ± 0 03	+15 ± 16	58 ± 19	32 ± 11	81 ± 1?
Group 2	–6 ± 13	+10 ± 17	0 32 ± 0 05	+2 ± 21	60 ± 4	43 ± 27	8? ± 7
Group 3	–3 ± 12	+10 ± 18	0 34 ± 0 07	+7 ± 12	53 ± 17	36 ± 7	94 ± 10
Normal values •	0 ± 13 (M) 0 ± 11 (F)	0 ± 10	0 35 ± 0 04	0 ± 14	71 ± 16	54 ± 9	

M = males F = females
Δ values represent the deviation of the measured values from normal
See text for details of abbreviations and indices

show a shortened ICT and ΔPEP an increased ΔLVET and a low PEP/LVET ratio

These data are in keeping with previous hemo dynamic studies of chronic anemia which show that peripheral resistance falls as a consequence of tissue hypoxia while venous return stroke volume, and cardiac output increase and the A V oxygen difference widens[19 21] During exercise there may be a further increase in myocardial contractility and cardiac output increases with out changes in LV end diastolic volume or pressure Coronary blood flow increases in relation to the increased cardiac output and supplies the additional myocardial oxygen demand[22] Ventricular enlargement and hypertrophy are compensatory mechanisms for the volume overload and do not necessarily imply impaired myocardial contractility On the contrary studies made in sickle cell anemia have shown that the left ventricle may tolerate volume overload for many years

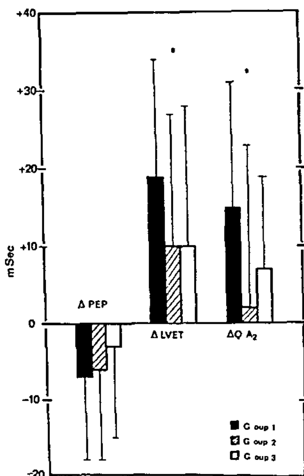


Fig 5 Systolic time interval measurements in the three groups of patients (mean ± 1 SD) expressed as the deviation from the normal rate corrected value ΔPEP is decreased ΔLVET increased and ΔQ A increased The changes are greater in Group 1 but the differences are not statistically significant

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indicates an incipient abnormality of LV systolic performance in the multiply transfused group, but these changes are small and are certainly not those of a severe congestive cardiomyopathy

Most patients in the study were in clinical 'congestive heart failure' with large hearts and a high jugular venous pressure *Diastolic function of the LV* is difficult to quantitate by non invasive technique but the smaller increase in EF slope and CE amplitude in patients who had received multiple transfusions may indicate an abnormality of compliance especially since these patients have the highest stroke and cardiac indices A short PR – AC time is present in some patients indicating, in them, increased LV end diastolic pressures[13] We believe, then, that the high filling pressures and the clinical 'congestive heart failure' which occurs in patients with thalassemia is predominantly the result of ventricular volume overload[7] with possible additional changes in ventricular distensibility due to hypertrophy,[8] iron deposition, and myocardial fibrosis of volume overload and abnormal chamber compliance There was no evidence in this study of a congestive cardiomoypathy

Summary

Left ventricular performance was studied in 23 young patients with severe chronic anemia due to β thalassemia major and intermedia The patients were divided into three groups according to the number of blood transfusions they had received The left ventricle (LV) was enlarged in patients who had not received blood and larger still in patients who had received multiple transfusions Echocardiography and systolic time interval measurements showed that systolic function of the LV was good in all the patients and that there was no statistical difference in systolic function in patients who had and those who had not received multiple transfusions Heart rate was increased in the latter group Stroke index and cardiac index were high especially in patients in Group 3 The diastolic closure rate (EF slope) of the anterior mitral leaflet and its amplitude of movement were increased but less so in Group 3 this may reflect an alteration in diastolic LV distensibility The results indicate that despite the presence of cardiomegaly and severe clinical congestive heart failure LV performance is well preserved in patients with β thalassemia, even in those who have received repeated blood transfusions Clinical cardiac failure is the consequence

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Hemodynamics of essential hypertension in young subjects*

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Contrary to the widely held belief that essential hypertension is rare among the young,[1] there is now evidence that it may occur at an early age[2] and account for a sizable proportion of hypertension even in children Estimates vary from 10 per cent to 93 per cent [3-6] The importance of these observations was recently stressed by the Report of the Task Force on Blood Pressure Control in Children [7] Since essential hypertension (EH) in children and adolescents may represent the early stage of the disease[5,6] with no, or minimal, complicating factors, its study at this young age would help to delineate more clearly variations in the individual hemodynamic factors and their functional interrelationship Thus, it would provide information to better understand the genesis of EH The practical importance of such a study derives from the seriousness of a diagnosis which entails lifelong therapy and from the fact that understanding the factors involved will help select rational therapy to provide better arterial pressure control with minimal side effects

This report describes hemodynamic and blood volume variations encountered among 42 young essential hypertensive subjects Findings were evaluated in relation to arterial pressure levels obtained both from intraarterial readings at the time of study and from weekly average of four daily determinations The difference between the two pressure levels allowed an estimate of the effect of invasive techniques on hemodynamic indices

From the Research Division The Cleveland Clinic Foundation Cleveland Ohio

This study was supported in part by grant HL6835 from the National Heart, Lung and Blood Institute National Institutes of Health Bethesda Md

Received for publication Dec 21 1977

Accepted for publication Jan 27 1978

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This study was presented at the Third Pediatric Nephrology Seminar January 5-8 1976 and the data detailed here were referred to in the Proceedings of that seminar

Material and Methods

The investigation involved 42 young hypertensive patients (37 males and five females) ranging in age between 15 and 25 years They were classified into the following groups (Table I) Group I included 13 patients younger than 20 years, they were all males Group II was made up of the older 29 patients (20 to 25 years), Group IIa included 24 males and Group IIb was composed of five females The diagnosis of hypertension was based on the readings recorded by their referring physician as well as the levels obtained on the hospital admission examination A blood pressure level exceeding 140/90 was considered abnormal this critical level corresponded approximately to the 95 percentile limits for adolescents blood pressure shown in the nomogram presented in the Task Force Report in 1977 [7] Some of these initial blood pressure readings were normal (< 140/90) in 17 patients whereas in the remaining 25 all the readings obtained by either their physicians or at the time of admission to the hospital were higher than 140/90 mm Hg In the hospital supine brachial arterial pressure was measured four times a day, using a sphygmomanometer cuff of proper size (⅔ arm length) The response of blood pressure levels to hospitalization was evaluated against the initial physician or admission reading

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Table I Patients investigated—42 essential hypertensives (15 to 25 years)

Group	Age group (years)	Number	Sex	Arterial pressure (mm Hg)
I	15 19	13	Male	1?6/81 167/104
IIa	20-25	24	Male	123/74 180/122
IIb	?0-25	5	Female	115/83-185/121

In all subjects extensive investigations including renal arteriography failed to reveal one of the known causes of hypertension

Hemodynamic studies All hemodynamic studies were done in the morning after an overnight fast and without sedation The details of the procedure were explained to the patient the day before and consent was obtained from the patient or his or her parents Cardiac output (CO) was determined in all 42 subjects but blood volume was obtained in only 34 five females and 29 males

Blood volume was determined after at least 30 minutes of supine rest using [125]I HSA and a 10 minute equilibration period Total blood volume (TBV) was calculated from plasma volume and simultaneously determined hematocrit with appropriate correction for the difference between total body and large vessel hematocrit Values were expressed in relation to body surface area as well as to body height

Cardiac output (indocyanine green dye) was determined in triplicate immediately following the plasma volume measurement The details of the procedure have been previously described in detail [6,7] Arterial blood pressure was recorded continuously from a catheter introduced percutaneously (modified Seldinger technique) through the brachial artery to the subclavian artery or to the root of the ascending aorta The derived parameters were calculated by classical formulae

Moreover an index or aortic resistance to stretch was calculated from the ratio of pulse pressure to stroke volume (PP/SV mm Hg/ml) This ratio which was found to be a clinically applicable index of aortic compliance is closely related to age level of diastolic pressure and heart rate values from previous investigation of 76 subjects allowed the development of a nomogram based on the following multiple regression analysis [2]

Table II Blood volume in 34 essential hypertensive patients (15 to 25 years)

	Male (29)		Female (5)
	15 19 yrs (9)	20 25 yrs (20)	20 25 yrs
PV			
ml/cm	16 4 ± 0 79	16 9 ± 0 58	13 9 ± 1 35
% N	88 ± 4.24	90 ± 3 11	90 ± 8 74
L/M	1 53 ± 0 69	1 48 ± 0 40	1 43 ± 0 14
% N	88 ± 3 96	85 ± 2.33	89 ± 9.01
TBV			
mL/cm	27 4 ± 1 44	29 1 ± 1 00	22 0 ± 1 87
% N	89 ± 4 62	94 ± 3 22	91 ± 7 69
L/M	2 55 ± 0 12	2.56 ± 0 73	2.26 ± 0 19
% N	93 ± 4 44	94 ± 2 65	91 ± 7 62

$$PP/SV = (0.0069 \text{ age} + 0.0048 \text{ DBP} + 0.009 \text{ HR} - 0.64) \pm 0.18$$

Since young people may often have undue elevations of systolic pressure the diagnosis of systolic hypertension was based on the following expected ratio of systolic to diastolic blood pressure

$$SBP = (DBP - 15) \times 2$$

Standard statistical methods were used to calculate t test χ and correlation coefficient and assess their statistical significance [5]

Results

The age sex and blood pressure range for each group are shown in Table I The pressures reported are the averages of four daily readings for a week in the hospital These varied among subjects from as low as 115/83 to as high as 185/121

Blood volume and plasma volume results were expressed in relation to both height (ml/cm) and body surface area (L/M[2]) to avoid the marked influence of body fat variations on the expression ml/Kg [6] Moreover values were also calculated in per cent of normal to allow comparison between sex groups [9,10] Average values were significantly below normal (Table II) However a study of blood volume distribution showed that although 61 per cent of the patients 20 to 25 years of age were hypovolemic 20 per cent fell within the normal range (91 to 109 per cent N) and there was a definite hypervolemic group (20 per cent of the patients) the per cent distribution among the nine younger patients was 67 per cent 22 per cent

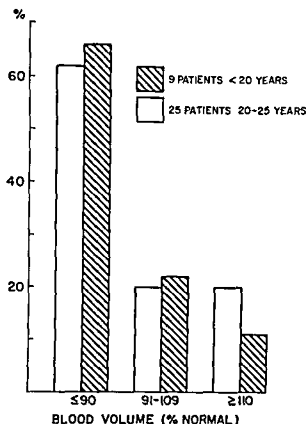


Fig 1 Blood volume distribution among 34 essential hypertensive patients aged 15 to 25 years Blood volume expressed in per cent of normal for our laboratory to allow comparison between sex groups In both the younger (15 to 19 years) and older (20 to 25 years) age groups the majority of patients were hypovolemic (< 90 per cent N) but there was also a small hypervolemic subtype (> 110 per cent)

and 11 per cent, respectively (Fig 1) This distribution was established on the basis of normal values derived from older subjects in our unit (20 to 60 years) However, blood volume values are reported in most references without distinction as to age subjects are grouped together from age 10 to 70 without qualification[21] Chien and associates[17] reported no change in blood volume expressed in milliliters per centimeter height over a 17 year follow up of the same subjects

In contrast to blood volume cardiac output was reported to be significantly lower with increasing age from 19 to 86 years[22] Our patients were therefore subdivided into two groups below 20 years and from 20 to 25 years There was no statistically significant difference between levels of blood pressure, heart rate cardiac index or total peripheral resistance in the two groups (Table III) Comparing these values to the normal adult values of our laboratory (CI 3 0 ± 0 5 L /min /M², TPR 29 ± 7 u M²) both groups had a higher CO but normal TPR Contrariwise, compared to results obtained from

Table III Hemodynamic indices (42 essential hypertensive subjects)

Index	*Age group*	
	15 20 yrs (13)	*20-25 yrs (29)*
MAP (mm Hg)	102 ± 2 86 †	110 ± 2 43
HR (b /min)	76 ± 4 34	78 ± 2 77
CI (L /min /M²)	3 31 ± 0 24	3 4[illegible] ± 0 1[illegible]
SI (ml /M²)	44 ± 2 79	45 ± 1 67
TPR (u M²)	32 ± 1 86	33 ± 1 48

Values reported as mean ± SE
†None of the differences was statistically significant

literature for patients of similar age group and younger,[23,24] the cardiac output of these young hypertensive subjects was found lower and total peripheral resistance was higher However, such comparisons are rather unsatisfactory because of differences in methods between various laboratories To evaluate the significance of cardiac output findings, various approaches were used First a histogram was drawn of the spread of cardiac output in this young essential hypertensive population (Fig 2) it demonstrated a relatively normal distribution ranging from 2 2 to 5.2 L /min /M² Secondly, cardiac output was evaluated in relation to arterial blood pressure level calculated in three different ways, namely the weekly pressure average (BP_a), the intra arterial pressure records (BP_i) during the study, and lastly the difference between these two levels of arterial pressure As regards weekly pressure averages there was no correlation between either systolic or diastolic levels and cardiac index in either the younger group (r = 0 331 for SBP and 0 325 for DBP) or the older group (r = 0 239 for SBP and 0 113 for DBP) Similarly, no correlation was found between intra arterial pressure and cardiac index in the 20 to 25 year old group (r = 0 163 for SBP and 0 048 for DBP) and only a weak correlation of borderline significance (r = 0 594 and 0 559 respectively, p < 0 05) in the younger patients (Fig 3)

The comparison of BP_a and BP_i revealed important contrasts The group means for intra arterial pressure (BP_{ia}) and for the weekly average (BP) were not markedly different diastolic blood pressure levels were practically identical (87 8 mm Hg and 87 3 mm Hg respectively) and systolic levels showed a slight difference (145 5

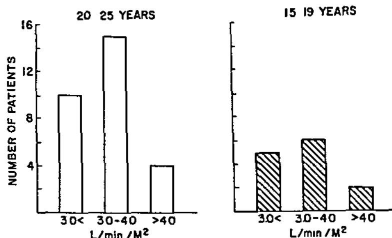


Fig 2 A histogram of cardiac output values corrected for body surface area in 42 essential hypertensive patients aged 15 to ?5 years The control value (3 to 4 L./min /M) was chosen on the basis of studies in normal young subjects [34]

Table IV Blood volume and cardiac output (34 young essential hypertensive subjects)

	Total blood volume (%N)		
	≤ 90%	*91 109%*	*≥ 110%*
Number	21	7	6
BP (mm. Hg)†	137/86 ± 2 15/1 35	133/86 ± 4 02/3 66	138/90 ± 6.31/5 23
BP (mm. Hg)†	148/89 ± 4 ?4/3 28	139/84 ± 2 65/2 74	141/89 ± 7.20/2 ?0
HR (b /min)	80 ± 3 8?	?0 ± 1 64	72 ± 5.84
CI (L./min./M)	3 27 ± 0 13	3 31 ± 0 17	2 95 ± 0 27
SI (ml./M)	4? ± 1 81	47 ± 3 08	42 ± 2 70
TPR (u M)	34 ± 1 58	31 ± 2 44	38 ± 3 74

Blood volume xpressed as pe cent of normal for ou lab ratory to ll w inclu n of b th se es
†Blood pressure reported in two w y BP –th g of four d ily eadings during week in hosp tal BP –th int arterial lev l obtained during th hemodynami t dy
N ne f the diff rences was tatist lly signifi ant

mm Hg ± vs 138 mm Hg ± $p < 0\,05$) This closeness of the means however obscured wider individual variations so that there was no significant correlation between the BP_i and BP for either systolic or diastolic level (Fig 4) The difference between the intra arterial pressure and the week s average (BP_i – BP) was considered an index of the effect of the invasive technique over the wide variation observed in this index (–30 to +40 mm Hg for SBP and –15 to +31 mm Hg for DBP) there was no correlation between cardiac index and the pressure effect of the test (r = 0 2403 and 0 1101 respectively) (Fig 5)

A comparison of the hemodynamic data classified according to the magnitude of blood volume showed that there was no significant difference among the three groups of normo hypo and hypervolemic patients (Table IV) In fact the hypervolemic patients tended to have if any thing a lower cardiac index (2 95 vs 3 27 L /min / M and a higher total peripheral resistance (38 vs 34 u M) than the hypovolemic patients

The index of aortic resistance to stretch was beyond one standard deviation in 10 patients whereas it was less than one standard deviation in only five suggesting that evidence for impaired aortic distensibility can be found in young people (Table V) This observation was further substantiated by analysis of six patients with pronounced elevation of systolic blood pressure Among these patients stroke volume varied from low normal to high normal only in one was it above two standard deviation of the mean On the other hand the aortic index was increased well above two standard deviation in three patients (Table

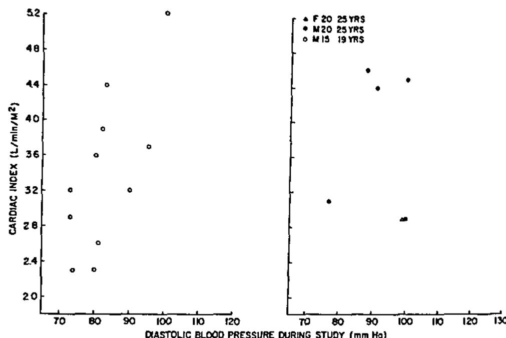


Fig 3 No correlation was found in the group aged 20 to 25 years (r = 0 048) between cardiac index and intra arterial pressure either systolic or diastolic Only the diastolic levels are demonstrated in this graph However a correlation of borderline significance (r = 0 559) was found in the younger group (15 to 19 years)

Table V Aortic distensibility in young hypertensive subjects (Index of aortic rigidity calculated as PP/SV mm Hg/ml *)

Patients (42)	Distribution of PP/SV Values		
	> 1 SD	within 1 SD	< 1 SD
Number	10	27	5
Per cent	24	64	12

Index of aortic resistance to stretch (PP/SV mm Hg/ml) compared with expected values obtained from a multiple regression equation developed from studies in 76 subjects
PP/SV = (0 0069 age + 0 0048 DBP + 0 009 HR − 0 64) ± 0 18

Table VI Systolic hypertension in six hypertensive patients aged less than 25 years

Patient	Aortic index mm Hg/ml		Stroke index
	Expected (± 0 18)	Actual	(N 45 ± 7 mL/M)
1	0 65	1 35†	38
2	0 47	0 50	60
3	0 71	1 12†	36
4	0 55	0 63	56
5	0 54	0 59	57
6	0 39	0 80†	4?

For definition see Table V
†Result > 2 SD expected value

VI) Systolic hypertension in patients younger than 25 years is therefore not uniformly due to an elevated stroke index

Discussion

Although the relationship of flow and pressure has been widely studied in normal adults and adult patients with essential hypertension [5, 28] only a limited amount of information is available concerning normal children [23, 24] This may be related to the obvious difficulties associated with hemodynamic studies in young subjects

It is only recently that the problem of essential hypertension in children and adolescents has received great interest [2, 4, 5, 7, 29, 31] However, ethical problems associated with invasive studies in young asymptomatic subjects have limited the number of hemodynamic studies in this age group Moreover, the diagnostic criteria as well as the expression of results present problems of their own In fact, the diagnosis of hypertension in young people has been often uncertain because of the lack of a common standard and because of the fluctuation in blood pressure Londe and colleagues[3] pointed out that criteria for blood pressure elevation led to the practical conclusion that any outpatient blood pressure reading above 140/90 can be considered abnormal for children older than 15 years This is in close agreement with the recent nomogram of blood pressure and age presented in the Task Force Report [7]

In our study a patient was included in the

hypertensive group if three abnormal readings were obtained at different times Although Page and associates[32] suggested that the diastolic blood pressure is more stable than the systolic other authors[33] pointed out that both levels may be equally responsive in children to emotional situations As far as this tension factor is concerned Loggie[4] has recommended that the blood pressure of children with high office readings be measured by their parents in more familiar conditions before the diagnosis of hypertension is established. Seventeen of our patients had normal blood pressure when calculated for the week from daily readings in the hospital This normalization of blood pressure in the hospital has been previously recorded both in adults and in children[30, 33, 36] This did not alter our diagnosis in such patients because neither the full implications of a blood pressure fall during hospitalization nor the normal range of values for hospitalized patients are well established[30]

Expression of hemodynamic results is particularly difficult in children because of variations in body size Weight alone does not take into consideration differences due to fatness or muscularity Height alone has been favored by Chien and coworkers[17] and by Tarazi and colleagues[18] as regards expression of blood volume values because it avoids the effects of obesity and of sex differences Moreover Chien and colleagues found that this expression gives stable values independent of age However body height alone does not take into account the metabolic demands of fatty tissue[37] Body surface area which combines both height and weight seemed more appropriate [3] although far from ideal[38] For our patients blood volume was calculated in relation to both height and body surface area while cardiac output was referred to the traditionally accepted reference of body surface area

Blood volume There was a spectrum of variation in the blood volume values among our patients from hypo to hypervolemic with a tendency to hypovolemia The occurrence of this variability in blood volume levels (as well as cardiac output levels) introduced a new aspect to the consideration of adolescent essential hypertension On the assumption that hypertension in the young represents an early phase of the disease it was expected that its study in the young might reveal a more homogeneous picture

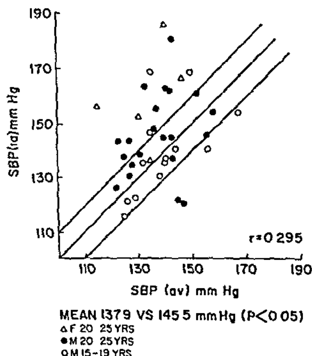


Fig 4 In these 42 young essential hypertensive patients, no correlation was found between intraarterial pressure levels obtained during the hemodynamic study (BP) and the pressure average (BP) calculated for the week of that study The diagonal lines represent the line of identity ± 10 mm Hg Only systolic pressures are illustrated in the graph the diastolic pressures gave similar results. The lack of correlation between BP_i and BP contrasts with the closeness of the averages (138 vs 146 mm Hg) and their small difference of borderline significance

than in adults because of the absence of complicating factors However the above results show that the classification of untreated essential hypertension in adults into hypo normo and hypervolemic subjects [0, 14] seems to extend to the young The volume-expanded group might represent diuretic responsive patients equivalent to the volume dependent adult hypertensive patients Only long term studies will demonstrate whether the different types remain true to themselves or if a hypovolemic patient will turn into hypervolemic and vice versa

Cardiac output Not only blood volume levels, but also hemodynamic characteristics in these young essential hypertensive patients were found to be as varied as among adults Cardiac index in young hypertensive subjects was not uniformly increased contrary to what would be expected from published studies of the early stages of essential hypertension [2, 6, 7] Its level varied from 2 2 to 5 2 L/min/M^2 this wide range introduced

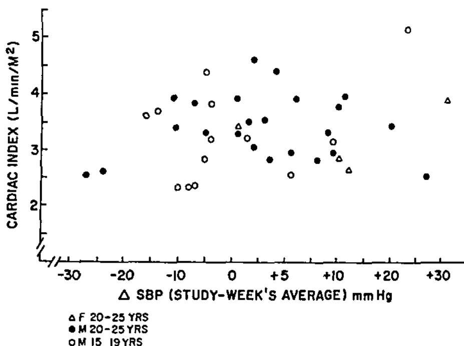


Fig 5 Blood pressure change associated with the hemodynamic study is expressed as the difference between the intra arterial pressure recorded during the study (BP) and the pressure average for that week (BP) Only systolic blood pressure is shown in the graph Over the wide range of blood pressure variation (−30 to +40 mm Hg) there was no correlation between difference in pressure and cardiac index indicating that the alteration in blood pressure was not necessarily dependent on the level of cardiac output

new elements for data evaluation There are greater difficulties in interpreting cardiac output levels than blood volume values, not only because cardiac output could be influenced by the tension of invasive procedures,[48] but also because of its variability with age For these reasons, analysis of cardiac output data was undertaken in relation to two other hemodynamic parameters blood volume and arterial pressure

1 As regards blood volume the magnitude of volemia did not seem to be the major determinant of cardiac output among young hypertensives because output values in the three groups studied (hypo , normo and hypervolemic subjects) were not statistically different If anything the hyper volemic group tended to have a lower cardiac output compared to the hypovolemic group It has been previously shown that cardiac index was not in direct relation to the degree of volemia [44] It would be therefore difficult to explain volume dependent hypertension on the basis of increased flow alone [49]

2 As regards arterial pressure an analysis of data in relation to one value alone is in our opinion incomplete because of the marked vari ability of pressure levels Indeed there was no correlation between blood pressure measured during the hemodynamic study and the hospital blood pressure average for the week of the hemo dynamic study (Fig 4) Both pressure levels as well as their difference were therefore, used to evaluate cardiac output in our patients None of the approaches revealed a significant correlation between pressure and output The difference between intra arterial pressure during the hemo dynamic study (BP_{ia}) and the weekly hospital average was taken to represent the pressure response to the situational factors of the test This response showed no correlation with the level of output The consistent failure of all three approaches to find a significant correlation between cardiac output and blood pressure indi cates that essential hypertension in the young is not the homogeneous entity primarily related as was previously thought to a raised cardiac output

Aortic distensibility was reduced (index of aortic resistance to stretch > one standard devia tion of expected value corrected for age and blood pressure) in 10 (24 per cent) of 42 young hyperten sive patients These results suggest that impaired aortic compliance may develop at a young age Analysis of six young patients with undue systolic blood pressure elevation confirmed this impres sion Systolic hypertension in the young has usually been ascribed to increased stroke volume [50, 51] However, in our six young patients stroke volume was increased only in one while

aortic rigidity was markedly increased in three out of six One is left only to speculate regarding the reason for this abnormality Structural changes in the arterial wall with increased colla gen tissue similar to those described in young spontaneously hypertensive rats may be thought of[3] On the other hand Tarazi and Dustan[33] have previously suggested that an increased sympa thetic tone might diminish distensibility of the aorta and large arteries Future studies will certainly be needed to clarify such findings in young people

In conclusion the complexity of the hemody namic pattern of essential hypertension in our patients suggests that the subdivision of essential hypertension into various groups applies even to youths Of great importance would be the devel opment of normal standards for children and adolescents Non invasive techniques would be undoubtedly of valuable help not only for the study of normals but also for the follow up of a long term illness usually characterized by a markedly fluctuant course

Summary

Cardiac output was determined in 42 young essential hypertensives (15 to 25 yrs) values ranged from 3.86 to 10 30 L /minute These differ ences were not related to magnitude of volemia Correlation of output to weekly blood pressure average (BP) was not significant its relation ship to intraarterial pressure (BP_i) was not significant in 21 patients aged 20 to 25 and of borderline significance in 13 aged 15 to 19 Blood pressure changes associated with the study (BP_i −BP) were also not consistently related to cardiac output Six patients had systolic hyper tension only one had elevated stroke volume

These results outline as complex a picture in young essential hypertensives as in older subjects

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Congenital tricuspid incompetence simulating pulmonary atresia with intact ventricular septum a report of two cases

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Isolated severe tricuspid incompetence in the neonatal period is associated with cyanosis and massive cardiomegaly Although most reports of severe tricuspid incompetence in neonates emphasize the poor prognosis and high surgical mortality rate of these patients[2] Boucek and associates recently described a favorable course in four infants who were managed conservatively Since tricuspid incompetence may be associated with severe right ventricular outflow obstruction requiring prompt surgical intervention it is essential to distinguish patients with isolated tricuspid incompetence from those with associated severe right ventricular outflow tract obstruction As pulmonary blood flow may be markedly reduced in both groups differentiation can be difficult even with catheterization and angiography

We report two cases of congenital tricuspid incompetence in which severe right ventricular outflow tract obstruction was suspected incorrectly after cardiac catheterization in the first days after birth The management course and outcome of these two patients differed markedly

Case reports

Case No 1 Baby V D was the 3 3 kilogram product of an uncomplicated pregnancy and delivery Cyanosis and cardio respiratory distress were noted immediately after birth Chest roentgenograms showed massive cardiomegaly and an electro cardiogram showed right atrial and right ventricular hypertrophy The infant was intubated and placed on a respirator Digoxin and diuretic therapy were begun and she was transferred to the Intensive Care Nursery at The University of California Hospitals San Francisco

Physical examination showed a cyanotic infant with massive hepatomegaly The precordial impulse was active and diffuse Peripheral pulses and blood pressures were normal. The first heart sound was normal the second heart sound was single A to and fro Grade III/VI systolic and II/VI diastolic murmur was heard best at the lower left sternal border A descending aortic blood sample obtained from an umbilical artery catheter showed a PH of 6 8 PCO > 100 torr and PO of 30 torr while the infant breathed 100 per cent oxygen *After adjustment* in the respirator rate and cycling the PO remained at 30 torr but the pH was 7 44 and the PCO 36 torr in 40 per cent oxygen An echocardiogram showed right ventricular dilatation but no pulmonary valve echo was identified

Cardiac catheterization was performed and the pertinent physiologic data are listed in Table I A venous catheter could not be passed into the pulmonary artery The retrograde arterial catheter was passed into the left ventricle but did not pass through the ductus arteriosus into the pulmonary artery Oxygen saturation data showed a bidirectional atrial shunt and an aortic blood oxygen saturation of 66 per cent with the patient breathing 40 per cent oxygen Pulmonary venous desaturation could not be excluded as a cause of cyanosis as a pulmonary vein was not entered Right atrial mean pressure was normal, but the *v* wave exceeded the *a* wave The right and left ventricular systolic pressures were equal and no systolic pressure difference between the left ventricle and the aorta was recorded An angiogram in the right ventricular apex showed marked tricuspid incompetence right ventricular and right atrial enlargement a deformity of the right ventricular outflow tract *and no* opacification of the pulmonary arteries (Fig 1) An angiogram in the right ventricular infundibulum again failed to show opacification of pulmonary arterial structures (Fig) A left ventricular angiogram was normal An angiogram performed in the ascending aorta

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Received f r publicat Sept 27 1977
Accepted f pubh t n Oct 31 1977

Reprint req ests William Berma J M.D Department of Pediatrics, Hershey Med l Center H rshey P 17033

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Table I Catheterization data

Case	Age	Parameters measured	SVC	IVC	RA mean	RA a	RA v	RV	MPA	PV	LA mean	LA a	LA v	LV	AO
1	2 days	Pressure (mm Hg)			4	5	8	50/3	–		5	7	5	50/3	50 3
		Oxygen saturation (%)	37	40	53			52	–		56			60	60
														(PO$_2$ = 34 torr)	
2	2 days	Pressure (mm Hg)			4	6	5	40/6	–		4	5	5	75/[illegible]	[illegible]
		Oxygen saturation (%)	57	60	60			59	–	91	76			79	79
														(PO = 4[illegible] torr)	
	3 wks	Pressure (mm Hg)			2	5	4	35/4	20/5		2	2	5	90/4	
		Oxygen saturation (%)	50	68	64			67	67		94			94	

revealed a normal aortic root a normal coronary arterial tree no narrowing of the aortic isthmus and a moderate sized tortuous patent ductus arteriosus The right ventricular infundibulum was visualized faintly because of pulmonary regurgitation (Fig 3)

The angiograms were interpreted as showing severe right ventricular outflow tract obstruction with secondary tricuspid incompetence At surgery the pulmonary valve was not stenotic The tricuspid valve was then explored and found to be dysplastic with short chordae and multiple small myxomatous nodules on the free margins of the leaflets The atrial septal defect was closed and the aneurysmally dilated right ventricular outflow tract was resected The child was weaned from cardiopulmonary bypass but had a cardiac arrest shortly thereafter and could not be resuscitated Postmortem examination showed a dilated dysplastic tricuspid valve without evidence of Ebstein s malformation The pulmonary valve was normal

Case No 2 Baby F was the 3 36 kilogram product of an uncomplicated pregnancy and delivery Cyanosis tachypnea and tachycardia were noted within the first hours of life She was begun on digoxin and transferred to The Milton S Hershey Medical Center on the second day after birth

Physical examination showed a moderately cyanotic infant with normal pulses and peripheral blood pressures There was a prominent right ventricular impulse The first heart sound was normal the second sound was single There was a harsh Grade III/VI systolic murmur at the lower left sternal border Chest roentgenograms showed massive cardiomegaly and an electrocardiogram showed right atrial and right ventricular hypertrophy The echocardiogram showed right ventricular dilatation but a pulmonary valve could not be identified An arterial blood specimen obtained while the patient breathed room air showed a pH of 7 37 PO of 37 torr and PCO of 23 torr Cardiac catheterization was performed and the data are summarized in Table I The retrograde arterial catheter could not be passed through the ductus arteriosus Neither conventional nor balloon tipped catheters could be passed into the pulmonary artery from the right ventricular outflow tract Oxygen saturation data showed a slight reduction of pulmonary venous blood saturation and a moderate right to left atrial shunt The aortic blood oxygen saturation was 79 per cent while the infant breathed room air Right ventricular systolic pressure was slightly more than half the systemic arterial level Right atrial phasic and mean pressures were normal An angiogram in the right ventricular apex showed massive tricuspid incompetence an enlarged right atrium an enlarged right ventricle a deformed right ventricular outflow tract and no anterograde filling of the pulmonary arteries (Fig 4) An angiogram in the right ventricular infundibulum again failed to show opacification of pulmonary arteries (Fig 5) A left ventricular angiogram was normal An ascending aortogram showed filling of the pulmonary arterial system through a small tortuous patent ductus arteriosus The aortic isthmus was not narrow The coronary arterial tree appeared normal

Pulmonary atresia or critical pulmonic stenosis with secondary tricuspid incompetence were considered as possible diagnoses however the relatively mild elevation of right ventricular systolic pressure the relatively moderate decrease in aortic blood oxygen saturation and the similarity of the catheterization findings to that of patients with isolated congenital tricuspid incompetence prompted us to delay surgical intervention The infant was placed in an atmosphere of 40 per cent oxygen and this was gradually decreased to room air over 5 days as cyanosis and signs of congestive heart failure diminished

The infant was recatheterized at 3 weeks of age (Table I) No right to left atrial shunt was noted The right ventricular systolic pressure was 40 per cent of systemic and there was a 15 mm Hg systolic pressure gradient across the pulmonary valve A right ventricular angiogram showed a dilated chamber decreased wall motion mild tricuspid incompetence and normal opacification of the pulmonary arterial tree (Fig 6) The pulmonic valve leaflets appeared thickened but moved well A left ventricular angiogram showed that the ductus arteriosus had closed

Discussion

A variety of lesions may cause severe tricuspid incompetence in the neonate (Table II) Of neonates with these conditions only those with marked right ventricular outflow tract or left sided obstructive lesions are candidates for cardiac surgery Most of the others require supportive care including correction of pulmonary and/or metabolic abnormalities but will show improvement with medical management



Fig 1 Right ventricular angiogram in case No 1 showing massive tricuspid incompetence and no opacification of pulmonary arterial structures

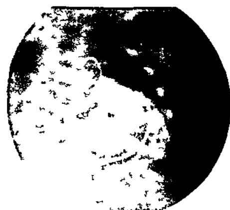


Fig 2 Right ventricular infundibular angiogram in case No 1 showing apparent pulmonary valve atresia



Fig 3 Aortogram in case No 1 howing tortuous ductus arteriosus (—>) pulmonic valve sinuses (- >) and faint pulmonary regurgitation (>)



Fig 4 Right ventricular angiogram in case No 2 showing massive tricuspid regurgitation, deformed right ventricular outflow tract and no opacification of pulmonary arterial structures

This is not necessarily the case with right ventricular outflow tract obstruction The patient with mild to moderate right ventricular outflow tract obstruction associated with a large patent ductus arteriosus may improve as the patent ductus arteriosus closes and the right ventricular after load falls On the other hand a patient with severe right ventricular outflow tract obstruction will become worse as the patent ductus arteriosus closes

Therefore identification of neonates with severe tricuspid incompetence associated with marked right ventricular outflow tract obstruction is essential especially since the right ventricular outflow tract obstruction can coexist with tricuspid valve dyspalsia[7] Occasionally differentiation can be made clinically or with the assistance of echocardiography however cardiac catheterization is usually required Even with cardiac catheterization and angiography exclusion of right ventricular outflow obstruction may be difficult In fact angiography may be misleading and prompt unnecessary surgery Of the two cases of congenital tricuspid incompetence



Fig 5 Lateral projection of right ventricular infundibular angiogram in case No 2 showing apparent pulmonary valve atresia



Fig 6 Right ventricular angiogram in case No 2 performed at age 3 weeks showing marked reduction in tricuspid incompetence and good opacification of pulmonary arterial structures

reported by Reisman and co workers[4] one was operated on for relief of suspected right ventricular outflow tract obstruction A normal pulmonary valve was found and the patient died during surgery Barr and co workers reported five neonates with tricuspid incompetence two of which were shown at surgery, to be unassociated with right ventricular outflow tract obstruction In each of those two cases the pulmonary artery was not entered at catheterization and right ventricular angiography failed to demonstrate patency of the pulmonic valve Both patients underwent surgery and died postoperatively Similarly, our first case died after surgery for relief of suspected right ventricular outflow tract obstruction

In contrast the correct diagnosis is readily established by catheterization and cineangiography in neonates with tricuspid incompetence secondary to left sided obstructive lesions elevated pulmonary vascular resistance or myocardial depression In each of these conditions usually the catheter can be passed into the pulmonary arteries and pulmonary arterial pressure can be recorded Moreover each of these lesions is associated with tricuspid incompetence which is acquired post natally Therefore the aortic isthmus shows the narrowing which is normal for the newborn infant[14] The main diagnostic problem is in differentiating those patients with tricuspid incompetence secondary to right ventricular outflow tract obstruction from those with the primary forms of tricuspid incompetence In these two groups the clinical features including physical examination electrocardiogram roentgenograms, and arterial blood gases may be similar Furthermore the limited pulmonary valve

Table II Classification of primary and secondary forms of tricuspid incompetence in the newborn infant

I. Tricuspid valve lesions (primary)
  A. Ebstein's malformation (5)
  B. Unguarded tricuspid valve (6)
  C. Tricuspid valve dysplasia (7)
  D. Endocardial cushion abnormality (8)
II. Conditions which can cause tricuspid incompetence (secondary)
  A. Severe right ventricular outflow tract obstruction (9)
  B. Transient tricuspid incompetence of the neonate (10)
  C. Marked elevation of pulmonary vascular resistance
    (1) persistence of fetal circulatory pattern (11)
    (2) severe pulmonary parenchymal disease (10)
    (3) upper airway obstruction (as choanal atresia) (12)
  D. Left sided obstructive cardiac lesions (10)
  E. Myocardial depression or dilatation from any cause (myocarditis, myocardiopathy, hypoglycemia, hypocalemia, hypoxemia, acidemia, etc.) (13)

motion or abnormal valve orientation in both groups may preclude identification of the pulmonary valve on echocardiogram. Cardiac catheterization findings also may be similar in the two groups. Since flow patterns may be similar in both groups, oxygen saturations may not be helpful in distinguishing them. Usually pulmonary artery pressures cannot be obtained and conclusions drawn from right ventricular pressures may be erroneous. Although right ventricular systolic pressures that are higher than systemic arterial levels suggest the presence of severe right ventricular outflow obstruction, a patient with mild or moderate pulmonary valve obstruction and a large patent ductus arteriosus also may have right ventricular systolic pressures above systemic levels. However, a patient with pulmonary atresia with intact ventricular septum, massive tricuspid incompetence, and low pulmonary blood flow may have right ventricular systolic pressures that are well below systemic levels. Right ventricular pressures at systemic arterial levels are common in pulmonary atresia with intact ventricular septum and have been reported also in neonates with isolated tricuspid incompetence.

The right ventricular angiograms show massive tricuspid incompetence and both groups may show no forward flow into the pulmonary arteries. Aortograms also show similar findings in both groups. The aortic isthmus does not show the narrowing noted normally in the newborn period. This lack of narrowing is associated with a decreased right ventricular forward flow *in utero* from any cause.[4] Furthermore, the angulation and tortuosity of the ductus are similar in both groups.

Passage of semi-rigid, wire-guided, or balloon-tipped catheters from the right ventricle to the pulmonary artery in these patients may be quite difficult; furthermore, if the right ventricular angiogram shows no forward flow, attempting such a maneuver is hazardous. Both of our cases, one of the cases reported by Reisman and associates, one of the cases reported by Kincaid and colleagues,[3] and two of the cases reported by Barr and collaborators[2] had diverticulum-like deformities of the right ventricular outflow tract that made manipulation of semi-rigid catheters into the main pulmonary artery difficult. The passage of balloon-tipped catheters into the pulmonary artery is usually not possible, as the regurgitation carries the inflated balloon back into the right atrium. Passage of a retrograde aortic catheter through the patent ductus arteriosus into the pulmonary artery is difficult because of the tortuosity and angulation of the ductus. Additionally, there is the hazard of the ductus constricting when stimulated by a catheter.

If the right ventricular angiogram shows marked tricuspid incompetence without pulmonary arterial opacification, it is crucial to determine whether or not the pulmonary valve is patent. Pulmonary regurgitation demonstrated on aortography excludes pulmonary atresia and is strong evidence against the presence of severe pulmonary stenosis. In addition, since a high pulmonary vascular resistance may retard pulmonary artery filling in some of the conditions under consideration, one might administer 100

per cent oxygen[16] or tolazoline[17] in an attempt to reduce pulmonary vascular resistance and promote pulmonary artery opacification on a right ventricular infundibular angiogram However, tolazoline is a potent systemic as well as pulmonary vasodilator, and its use is accompanied by some risk especially if the patent ductus arteriosus is the sole source of pulmonary blood flow Though both of our cases underwent right ventricular infundibular angiography without pulmonary artery filling, neither was given tolazoline or 100 per cent oxygen prior to angiography

As these cases illustrate, right ventricular outflow tract patency cannot be established at catheterization in some infants with severe isolated tricuspid incompetence Management may therefore be a problem Though surgical intervention often is mandatory when severe right ventricular outflow tract obstruction exists it has been ineffective in infants with isolated tricuspid incompetence These two cases and those reviewed in the literature suggest that a combination of findings is characteristic though not diagnostic, of infants with isolated tricuspid incompetence without right ventricular outflow tract obstruction These findings include

a large right ventricle,

right ventricular systolic pressures less than or equal to systemic

aortic blood oxygen saturations over 65 per cent levels higher than those found in most infants with pulmonary atresia or critical pulmonary stenosis and

a moderate sized diverticulum like deformity of the right ventricular outflow tract

Even when these factors are considered uncertainty may remain and diagnostic errors may occur Because of the apparent advantage of delaying surgical intervention in those infants without right ventricular outflow tract obstruction, intensive supportive care and observation should be instituted Oxygen therapy may reduce pulmonary vascular resistance and thereby promote anterograde pulmonary artery flow and improve aortic oxygen saturation Moreover if anterograde pulmonary blood flow increases a pulmonary valve echo may become visible on repeat echocardiography However, as long as the diagnosis remains unclear, prompt surgical treatment should be available for those infants whose clinical status deteriorates

Summary

Two infants with isolated congenital tricuspid incompetence appeared to have associated right ventricular outflow tract obstruction at diagnostic evaluation, including catheterization and cineangiography One infant died during surgery the other improved rapidly and survived with medical therapy We discuss the problem of establishing the presence of patency of the right ventricular outflow tract in infants with massive tricuspid incompetence and outline an approach to the management of infants whose diagnosis remains unclear even after careful evaluation

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Exposure of concealed right bundle branch block in Wolff-Parkinson-White type B by pacing from the vicinity of the A-V node

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Electrocardiographic concealment of right bundle branch block by the Wolff Parkinson White syndrome type B as well as the electrocardiographic patterns resulting from the coexistence of these two conduction abnormalities, have been attributed to the relationship between the location of the accessory pathway (septal or parietal) and the site of right bundle branch block (central of peripheral)[1] We recently have observed that pacing from the vicinity of the A V node may help to clarify and elucidate these phenomena

Material and methods

Two patients having exclusively Wolff Parkinson White type B conduction during sinus rhythm on the electrocardiogram and in whom the presence of right bundle branch block was not suspected form the basis of this report

An informed consent was obtained from the parents prior to electrophysiological studies In each patient the study was performed in a post absortive basal state under Demerol and Phenergan sedation[3] None of them had received cardiotonic or antiarrhythmic medication for at least 48 hours prior to the procedure A tetrapolar 5F electrode catheter (Elecath Corporation Rahway, New Jersey) was used to pace and record from different intracardiac sites The electrodes had a width of 2 mm The corresponding interelectrode distances were between one and two = 1 mm and between three and four = 5 mm Bipolar recording was performed through electrodes one and two and bipolar pacing through electrodes three and four

The corresponding electrograms filtered with a setting of 40 to 400 or 400 to 500 Hz were displayed simultaneously with three surface electrocardiographic Leads, usually I II, and V_1 on a multichannel oscilloscopic recorder (Electronics for Medicine DR 8 White Plains New York)

The electrode catheter was initially used to determine the site which, during atrial pacing resulted in the shortest St-delta interval There after the catheter was placed over the septal leaflet of the tricuspid valve to record a His bundle electrogram through the distal electrode pair Once His bundle activity was identified electrical stimulation was performed from the proximal electrode pair

Definition and measurement of P A A H and H V intervals were as conventionally described[3] Normal values in our laboratory for pediatric patients are 0 to 35 msec 50 to 115 msec and 30 to 45 msec respectively

The P-delta (or St-delta) intervals represented the time elapsing between onset of the P wave (or deliverance of the stimulus to an ectopic atrial site) and onset of ventricular depolarization

Case 1

A one year old female with an A V canal had an electrocardiogram which demonstrated Wolff Parkinson White type B without evidence of right bundle branch block during sinus

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Received for publication Oct 10 1977
Accepted for publication Nov 18, 1977

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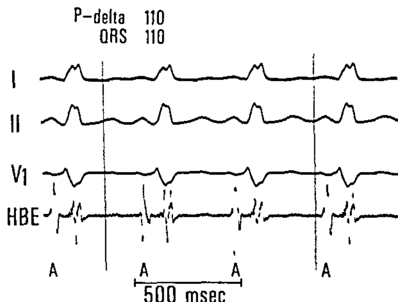


Fig 1 (Case 1) Wolff Parkinson White syndrome type B without evidence of right bundle branch block during sinus rhythm at a cycle length of 430 msec (rate of 139/minute) *HBE* = His bundle electrographic lead *A* = low septal right atrial electrogram

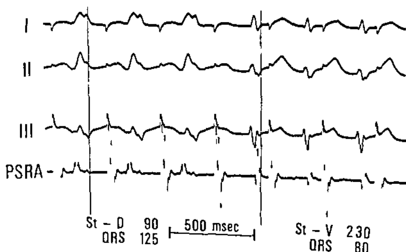


Fig 2 (Case 1) Atrial pacing from the posteroseptal right atrial *(PSRA)* site at a rate of 200 beats/minute resulted in conduction block in the accessory pathway with subsequent conduction over the normal pathway (left anterior hemiblock incomplete right bundle branch block pattern)

rhythm (Fig 1) The duration of the corresponding intervals measured at a sinus cycle length of 430 msec were as follows P-delta = 110 msec P A = 30 msec A-delta = 80 msec P-J interval = 220 msec and QRS duration = 110 msec The H deflection was incorporated within the ventricular electrogram recorded by the His bundle electrographic lead

Pacing from a posterolateral right atrial site resulted in the shortest St-delta interval 90 msec The ventricular complex was 15 msec. longer than during sinus rhythm Hence A V conduction was now taking place exclusively through the accessory pathway The P waves were positive in Leads I II and III A 1 1 A V conduction ratio persisted until the cycle length was reduced to 300 msec (rate of 200/minute) Thereafter propagation through the accessory pathway failed and the impulse was conducted exclusively via the normal (A V node-His Purkinje) pathway with a left anterior hemiblock incomplete right bundle branch block pattern (Fig 2) The St V intervals and QRS complexes measured 230 msec and 80 msec respectively

Since atrial pacing was performed from the vicinity of the

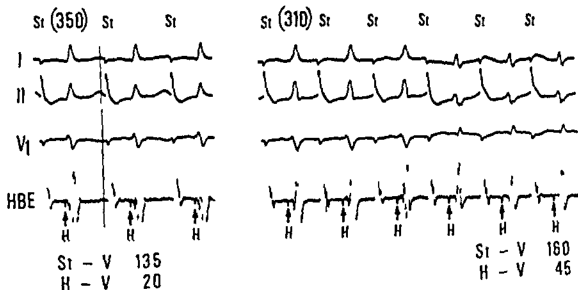


Fig 3 (Case 1) Pacing from the vicinity of the A V node resulting in fusion beats with (pseudo) normal QRS complexes and short H V interval at shorter cycle lengths (350 msec) than those at which exclusive accessory pathway conduction had occurred when pacing from close to the atrial entrance of the accessory pathway *(Fig 2)* Exclusive A V normal pathway conduction occurred toward the *end of the right sided panel*

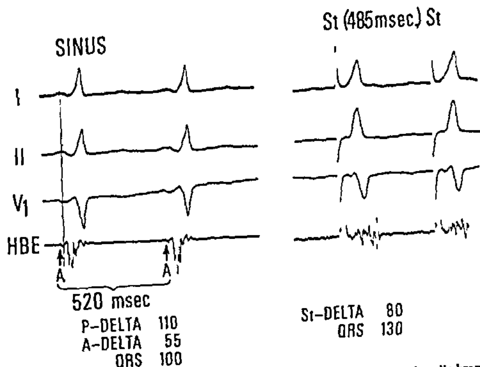


Fig 4 (Case 2) Wolff Parkinson White syndrome type B without evidence of right bundle branch block during sinus rhythm *(left sided panel)* and atrial stimulation from the site yielding the shortest St-delta interval *(right sided panel)*

atrial entrance of the accessory pathway the corresponding ventricular electrogram (recorded through the same catheter) presumably represented the electrical activity of the tissue in the area of the ventricular junction of the accessory pathway This is supported by inscription of the corresponding ventricular electrogram 50 to 10 msec *before* the onset of the QRS in the surface leads during exclusive accessory pathway conduction and 40 msec *after* the beginning of the QRS during normal pathway conduction as indicated in Fig 2

In contrast when pacing was performed from the vicinity of the A V node P waves were negative in Leads II III and aVF and slightly positive in Lead I (Fig 3 *left panel*) A progressive increase in the pacing rate revealed that the QRS complexes were apparently normal when the cycle length was decreased to 350 msec (rate of 182/minute) There was a qR morphology in Lead I with rS complexes in V1 The St V interval was normal for the rate (135 msec.) but the H V interval was short (20 msec)

A similar QRS morphology persisted until the cycle length was reduced to 310 msec (Fig 3 *right panel*) At this cycle length the left anterior hemiblock-incomplete right bundle branch block pattern appeared with St V and H V intervals of

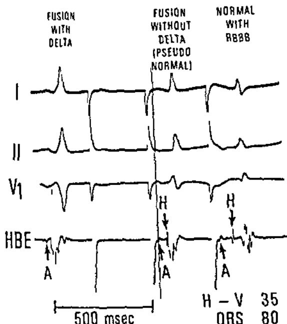


Fig 5 (Case 2) Sinus rhythm producing QRS complexes with delta wave and no evidence of right bundle branch block *(left)* and atrial pacing from the vicinity of the A V node producing a fusion QRS complex without delta wave (pseudo normal QRS complexes) and no evidence of right bundle branch block *(middle)* and QRS complexes resulting from exclusive conduction through the normal pathway with right bundle branch block *(left)*

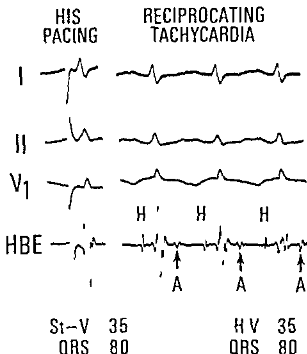


Fig 6 (Case 2) QRS complexes resulting from exclusive ventricular *activation through* the normal pathway during His bundle pacing *(left)* and A V reciprocating tachycardia *(right)*

160 msec and 45 msec respectively Thus, the ventricular complexes which seemed to have been narrow with a short H V interval of 20 msec (Fig 3 *left panel*) were fusion beats resulting from ventricular depolarization through both normal and accessory pathways In these beats the late ventricular activation (related to the right bundle branch block) was abolished by the right ventricular pre-excitation Of *note* the changes depicted in Fig 3 could have been attributed *to* tachycardia dependent block in the accessory pathway if only the surface leads had been recorded or pacing from another atrial site was not performed This *finding is* probably due to the early right ventricular excitation second ary to the shorter conduction time (from paced site to *the* ventricles) via the normal pathway

To summarize in this patient a Wolff Parkinson White type B pattern occurred during sinus rhythm and posteroseptal atrial pacing until the cycle length was *reduced to 310* msec at which time A V conduction via the normal pathway exposed a previously concealed incomplete right *bundle* branch block pattern In contrast pacing from the vicinity of the A V node pseudo-normalized the QRS complexes and produced a false pattern of tachycardia dependent block in the accessory pathway

Case 2

During sinus rhythm at a rate of 115/*minute* (cycle length of 520 msec.) this one year-old with recurrent tachyarrhythmias and no evidence of organic heart disease had electrocardiographic evidence of Wolff Parkinson White *type B* The P-delta interval measured 110 msec (Fig 4 *left panel)*

An H deflection was not seen because the interval between A and V (in the His bundle electro ardiographic lead) was *so short (55 msec)* that activation of the His bundle must have occurred within the corresponding ventricular deflection The *incomplete* left bundle bran h block pattern with a QRS duration of 100 msec suggested that the ventricular complexes were fusion beats resulting from activation *through* both *normal* and accessory pathways

Moreover *the* QRS duration increased to 130 msec when the mid to-low lateral right atrium was paced at a cycle length of 486 msec (rate 125/minute) as seen *in* the right panel of Fig 4 This was the site from which the shortest St delta interval was recorded (80 msec) As was observ*ed during* sinus rhythm the H deflections were lost within the ventricular electrogram of the His bundle electrocardiographic lead

Atrial stimulation in the proximity of the A V node produced various types of QRS complexes Those resulting from exclusive conduction through the A V node His Purkinje pathway showed a normal electrical axis R/s pattern in standard Lead I and an incomplete right bundle branch block pattern (rsR complexes) *in* V The duration of QRS complexes and H V intervals was 80 msec and 35 msec respectively (*last beat* in Fig 5) These beats had similar features to those recorded during reciprocating A V tachycardias and His bundle pacing (Fig 6) Note *that* the latter showed St V intervals and ventricular complexes similar to the H V interval and QRS pattern of beats conducted exclusively through the A V node

In addition multiple types of *fusion* beats were observed

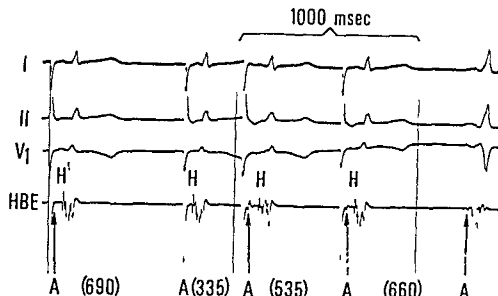


Fig 7 (Case 2) Pacing from the vicinity of the A V node and perhaps from the A V node itself *(second beat)* resulting in the QRS pattern suggestive of exclusive normal pathway conduction This occurred at cycle lengths which were both longer (690 msec) and shorter (535 and 335 msec) than those which during sinus rhythm (660 msec) or pacing from the atrial site resulted in the shortest St-delta interval producing a Wolff Parkinson White type B morphology without right bundle branch block *(Fig 4)*

Some (*second beat* in Fig 5) had a normal contour (qR pattern in Lead I and rS in V) with almost simultaneous inscription of H and V Others showed different degrees of incomplete right bundle branch block with shorter than normal (in the range of 0 to 30 msec) H V intervals (Fig 7) Absence of Wolff Parkinson White type B pattern during pacing from the vicinity of the A V node occurred at cycle lengths which were similar shorter or longer than those which *during sinus rhythm or pacing from the mid right* lateral atrium had produced Wolff Parkinson White type B (Fig 4) This phenomenon was related to the (peri A V nodal) site of stimulation and not to tachycardia or bradycardia dependent block in the accessory pathway

To summarize in this patient Wolff Parkinson White syndrome type B concealed the incomplete right bundle branch block during sinus rhythm and when pacing close to the atrial end of the accessory pathway The incomplete right bundle branch block pattern however was exposed by stimulation from the vicinity of the A V node which in addition produced inaccurate interpretations of surface electrocardiographic patterns of rate dependent block in the accessory pathway as well as pseudo normal QRS complexes

Discussion

Conventional electrocardiographic theory states that if Wolff Parkinson White type B is due to conduction through a right sided accessory pathway, the simultaneous features of Wolff Parkinson White type B and complete right bundle branch block should not occur since the right ventricular pre excitation is expected to mask the delayed right ventricular activation produced by the right bundle branch block [4] Yet, both processes are known to coexist [3,10] To explain their simultaneous occurrence it has been suggested that a central right bundle branch block should be concealed by a ' distal accessory pathway whereas a 'peripheral' right bundle branch block would not be hidden by a proximal ' accessory pathway [1]

The right bundle branch block pattern displayed by the two patients reported in this communication was probably of the 'peripheral type ' [3] It was also incomplete " in the sense that during normal pathway conduction some parts of the right ventricle could still be activated by a delayed wavefront emerging from the right bundle branch

Figs 1 through 7 show that the effects of a right sided accessory pathway on a right bundle branch block pattern also depended on the differences between the moment of arrival of excitation at the ventricular sites from which the corresponding wavefronts *emerged from the accessory* pathway and *from the normal pathway* (via the right and left bundle branches) as well as on the conduction time from these sites to the others These differences in turn were a function of several factors namely *duration* of the refractory periods and conduction times of the structures involved *rate* of supraventricular impulses and *pacing sites*

Reports discussing the effects of pacing sites on

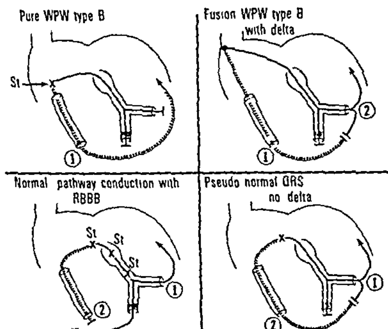


Fig 8 Diagrams depicting the various mechanisms whereby a Wolff Parkinson White syndrome type B can obscure a coexisting (peripheral) right bundle branch block See text for discussion

A V conduction and QRS pattern in Wolff Parkinson White syndrome have dealt mainly with the changes produced by stimulation from close to the atrial entrance of the accessory pathway that is the site which yields the shortest St-delta intervals for a given rate These studies explain why right atrial pacing produces shorter St V intervals in Wolff Parkinson White type B than left atrial (or coronary sinus) stimulation and why the reverse occurs in Wolff Parkinson White type A Decreasing the atrial contribution to the St V intervals is of particular importance in the presence of intra atrial conduction defects which can be considerably exaggerated by electrical stimulation

For instance in the *left side of the panel* of Fig 2 recorded during pacing in the proximity of the atrial end of the accessory pathway a pure Wolff Parkinson White type B pattern (without any evidence of right bundle branch block) occurred This was due to the fact that the wavefront traversing the accessory pathway was able to depolarize the corresponding right and left ventricular areas ahead of (thereby rendering them refractory to) the wavefront traversing the normal pathway (Fig 8 *top left*)

On the other hand fusion QRS complexes (with a delta wave but no evidence of right bundle branch block) were observed during sinus rhythm (Figs 1 and 3) when the wavefront traversing the accessory pathway reached the right ventricle before the wave front traversing the normal pathway (thus producing the delta wave) provided that it did not activate some left ventricular areas which were depolarized by the wave front emerging from the fascicles of the left bundle branch (Fig 8 *top right*)

In contrast Figs 2 5 and 7 show that atrial pacing from the vicinity of the A V node as well as His bundle stimulation (Fig 6) and perhaps A V nodal stimulation itself (*second beat* in Fig 7) produced the QRS pattern characteristic of normal pathway conduction with subsequent exposure of the right bundle branch block (Fig 8 *bottom left*) Apparently the wavefronts emerging from the bundle branches reached the ventricular end of the accessory pathway ahead of the wave front traversing the accessory pathway This could be due to either earlier arrival of excitation at the site of emergence from the bundle branches and/or to late arrival at the ventricular end of the accessory pathway The latter presumably was due to the delay in impulse propagaton from stimulated (peri A V nodal) site to atrial entrance of the accessory pathway

Occasionally pacing from the vicinity of the

A V node produced apparently normal ventricular complexes without a delta wave This even occurred with pacing rates which were slower than those which resulted in block in the accessory pathway when stimulation had been performed close to the atrial end of the accessory pathway (Figs 3 and 5) The normally appearing ventricular complexes were in reality fusion beats (Fig 8 *bottom right*) Although the wavefronts emerging from the fascicles of the left bundle branch were the first to depolarize the ventricles (thus explaining the absence of a delta wave), they *did not* reach the right ventricular end of the accessory pathway ahead of the wavefront traversing structure Thus the left ventricle was activated through the A V node His Purkinje pathway and right ventricle via the accessory pathway

Fig 8 summarizes the mechanism whereby right bundle branch block can remain concealed in certain patients with right sided accessory pathways when the QRS pattern is that of a fusion complex with or without delta waves, or pure Wolff Parkinson White type B or when the ventricular complexes appear to be normal "

On the other hand Figs 3, 5 and 7 show that pseudo tachycardia and pseudo bradycardia dependent block in the right sided accessory pathway (occurring during peri A V nodal pacing) most probably reflected a faster arrival of excitation at the A V node and consecutively at the sites of emergence from the bundle branches rather than an abnormal delay through the atria in reaching the accessory pathway However, both factors could have played a role

Summary

In two infants with Wolff Parkinson White type B right bundle branch block was concealed during sinus rhythm and pacing from close to the atrial entrance of the right sided accessory pathway However, pacing from the vicinity of the A V node the A V node itself, and the His bundle exposed the right bundle branch block by producing exclusive ventricular activation through the normal A V nodal His Purkinje pathway

In addition pacing from close to the A V node also resulted in fusion beats characterized by absence of delta waves with (pseudo) normal QRS complexes and short H V intervals False patterns of tachycardia dependent and bradycardia dependent block in the accessory pathway also occurred These dynamic phenomena were attributed to the (peri A V nodal) pacing related, relatively early arrival of excitation at the ventricles through the normal pathways coexisting with delayed arrival of excitation via the accessory pathway The latter in turn was due to the longer intra atrial conduction time from paced (peri A V nodal) site to atrial entrance of the accessory pathway

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Intraventricular conduction disturbances A review of prevalence etiology, and progression for ten years within a stable population of Israeli adult males

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The prevalence or right or left bundle branch block (RBBB or LBBB) has been studied repeatedly both in symptomatic and asymptomatic subjects during the last decades Little information is available however on the prevalence of other intraventricular conduction disturbances (IVCD) such as left anterior hemiblock (LAH) or RBBB + LAH In addition while it is well established that most patients with chronic complete heart block (CHB) suffer from a degenerative process affecting both bundle branches [3] the importance of the latter in producing other IVCD has not been hitherto evaluated Likewise the prevalence of a degenerative disease of the conduction system among the general population and its ECG evolution have received little attention so far Finally while numerous papers describe the clinical implications of right or left BBB in the ECG very few deal with the long term evolution of these patterns The only IVCD whose progression has been investigated and only for short follow up periods is RBBB + LAH while the progression of monofascicular blocks (RBBB or LAH) has been left completely unexplored

This study has elucidated the prevalence of various types of IVCD in a defined segment of the male population in Israel has determined some of the associated conditions and has followed the progression of the various forms of conduction disturbance during a 10 year period

All subjects were part of the population study of the Israeli Ischemic Heart Disease Project the details of which have been described elsewhere [10] Briefly a random sample of Israeli male civil service employees aged 40 years and over and working for the State or municipality in the Jerusalem Haifa and Tel Aviv areas were studied in 1963 (10 232 men) These patients were reexamined and had an ECG recorded in 1965 and 1968 In the present study the ECG tracings of 5 204 subjects (average age 49 8 years) representing participants from the Tel Aviv area only were reviewed and only those showing IVCD were retained There were 123 subjects who were invited for a further examination in 1973 thus achieving a 10 year follow up period (1963 to 1973) The mortality rate and follow up data are shown in Table I The average follow up period for the 104 survivors was 9 7 years

ECG criteria

ECG criteria for RBBB and LBBB were those of the ischemic heart disease project [1] as follows LBBB was diagnosed when QRS duration was 0 12 sec or more in any three leads and R duration 0 08 sec in Leads V_5 or V_6 and S duration 0 04 sec and T negative in Lead I or aV_L

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Received fo publi ation Sept. 14 19 7

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0002-8 03/78/11 10/0

Table I Prevalence mortality rate, and follow up in 123 patients with intraventricular conduction disturbances (IVCD) among 5 204 working adult males

Type of IVCD	Prevalence and age			Deaths		Survivors		
	No of patients	Prevalence in population	Average age (years)	No of patients	Average follow up period till death (years)	No of patients: Survived	No of patients: Incomplete follow up	Average follow up period for survivors (years)
LAH*	74 (60%)	1 42%	53 2	10	6 3	64	4 (5 years)	9
RBBB	34 (28%)	0 65%	53 5	4	6 5	30	2(2 5 years)	9 6
RBBB + LAH	9 (7%)	0 17%	58 2	1	8	8		10
LBBB*	6 (5%)	0 12%	53 7	4	3 2	2		10
Total	123 (100%)	2 36%	53 5	19(15%)	5 8	104	6	9

LAH left anterior hemiblock RBBB right bundle branch block LBBB left bundle branch block

Table II Prevalence of IVCD according to age

Age in years	40 44	45 49	50 54	55 59	60+	Total
No of subjects	1716	1090	1128	772	498	5204
No of patients with IVCD	16	16	34	36	21	123
Prevalence	0 93%	1 47%	3 01%	4 66%	4 22%	2 36%

and no Q in V or V_6 RBBB was diagnosed when QRS was 0 12 sec or more in any two standard leads and S duration 0 04 sec or more in Lead I or aV_L and R' or QR present in V_1 or V_2 ECG criteria for LAH were based on those or Rosen baum and others[6 ,] and included the follow ing mean frontal plane electrical axis of the QRS between –45 degrees and –90 degrees small q wave in aV_L with rS pattern in Leads II III aV_F (or qrS pattern in case of diaphragmatic myocar dial infarction) and QRS duration not exceeding 0 10 sec in any lead Patients with cor pulmonale and low voltage (25 patients with R or S less than 5 mm in any lead) or with pectus excavatus (three patients) were excluded in order to avoid false positive diagnosis of LAH The criteria for left posterior hemiblock (LPH) were[13 15 16] mean frontal plane electrical axis +120 degrees rS pattern in Leads I, aV_L and QR pattern in Leads II III aV_F provided that these were found in an obese stocky person over 45 years of age without evidence of right ventricular hypertrophy and when some form of left ventricular disease is present (this could not be diagnosed with certain ty in any of our cases) The criteria for RBBB + LAH were[ ] a mean QRS axis between –45 degrees and –120 degrees in the presence of RBBB Bilateral bundle branch block (BBBB) was diagnosed when both criteria for RBBB and LBBB were present in the same recording[17] The method for determining the mean frontal plane QRS axis was that of Laiken and colleagues[ ] taking the average of values obtained for each of three pairs of leads for each recording

Progression of conduction disturbances was diagnosed by the appearance of either a P R prolongation (> 0 22) or an added fascicular block or complete heart block (CHB)

Other criteria

A diagnosis of ischemic heart disease (IHD) was made according to the criteria of the Ischemic Heart Disease Project[11] and included (1) all subjects with definite angina pectoris (2) all subjects whose previous history of heart attack was verified and (3) all subjects with an ECG diagnosis of probable infarct

The diagnosis of hypertension (HT) was retained only when diastolic pressure measure ments were 100 mm Hg or over on two occa sions

Prevalence

The prevalence of RBBB or LBBB in different populations has been the subject of numerous investigations The frequency of *RBBB* was found to be the lowest among young healthy individuals mostly aircraft personnel or appli cants being 0 15 per cent to 0 29 per cent[ ] The figure increases sharply with age even in a healthy population reaching 2 4 per cent in selectively old populations (retirement communi

Table III Natural history of IVCD (15 patients)—progression according to ECG

Initial IVCD	No of patients	No of patients showing progression			
		to BFB	to BFB and CHB	to CHB without BFB	Total
LAH	74	5	1	1	7 (9 5%)
RBBB	34	5	2	1	8 (22 5%)
Total	108	10	3	2	15 (14%)

BFB-bifascicular block CHB-complete heart block

ty) aged 52 years or more[2] Among symptomatic subjects usually outpatient populations RBBB was seen as frequently as in 1 15 per cent to 3 19 per cent[2] While our figure of 0 65 per cent (Table I) is much higher than among the above young selected asymptomatic patients series it is as expected much lower than among symptomatic subjects The only comparable general population study is that of Ostrander about the Tecumseh community[6] In this the prevalence of RBBB was only 0 2 per cent that is markedly lower than ours However about half the subjects of the latter study were under the age of 20 and only 27 per cent were above the age of 40

LBBB seems to be extremely rare among young and healthy subjects Thus among aircraft personnel and applicants its average prevalence was between 0 02 per cent and 0 05 per cent[2] [3] [2] In younger age groups of the same population it was practically absent [3] [8] However among elderly or symptomatic subjects the frequency of LBBB was much higher 1 0 to 1 2 per cent In the Tecumseh community it was equal to the frequency of RBBB (0 2 per cent) surprisingly high for this relatively young population for which we have no explanation Our figure of 0 12 per cent is as expected somewhat higher than among aircraft personnel but far lower than among old or symptomatic subjects

As for *LAH* review of the English literature discloses very little data on its prevalence More information is available concerning left axis deviation (LAD) without definite criteria of LAH Grant[9] in a pioneer work on LAD examined the ECG tracing recorded during the last week of life of unselected patients coming to autopsy and found an axis of −15 degrees or to its left in 20 per cent This very high frequency can be ascribed to the strong bias introduced by the selection of fatal cases Among young healthy aircraft personnel (aged 18 to 32 years) LAD of −30 degrees or to its left was found in 0 2 to 1 2 per cent [31] while among two series of adults (aged 45 to 69 years and above 20 respectively) LAD (< −30 degrees) was found in as many as 4 1 and 5 3 per cent respectively[3] [33] These series confirm that the QRS axis has a leftward tendency with age[19] [3] [33] [35] An exceptionally high frequency of LAD (−30 degrees to −90 degrees) probably due to a genetic factor was recorded among the Navajo children (10 per cent)[36] As far as true LAH is concerned we are aware of only two epidemiologic studies one by Rosenbaum and associates[2] who found LAH in 76 out of 1658 patients (4 58 per cent) attending their cardiological service and the other by Yano and associates[3] who detected LAH in 1 5 per cent of 8 000 adult Japanese American men in Honolulu The latter is the only study on general adult male population and its findings are strikingly similar to ours (1 4 per cent Table I)

Table IV Natural history of IVCD (15 patients)—progression according to etiology

Etiology	Total no of patients	Patients showing progression	
		No of patients	Average age (years)
IHD	35	5 (14%)	50 6
HT	24	5 (21%)	59 4
None	64	5 (8%)	49 6

Details in Tables VI VII nd VIII

The prevalence of *RBBB + LAH* in the general population is practically unknown It was not investigated in the above mentioned air forces series because most had been studied before this IVCD was recognized The only similar and recent study is that of Rotman and colleagues[3] who found this pattern in 0 008 per cent of aircraft personnel and applicants Among hospitalized patients the prevalence of this BFB was

Table V Progression of ECG pattern in 5 patients with IHD

Patient No	*Age (years)*	*Initial IVCD*	*Time of appearance (years)*		*Remarks*
			BFB	*CHB*	
1	52	LAH	–	7	CHB during AMI (fatal outcome despite pacemaker insertion
2	54	LAH	5 (BBBB)	–	Previous AMI in 1952
3	52	RBBB	4 (BBBB)	8	AMI in 1952 1958 and 1968 PR> since 1970 Died 1971 despite pacemaker insertion
4	48	RBBB	5	–	AMI in 1960 and 1972 PR> since 1972
5	47	LAH	5	–	Anginal syndrome since 1968

AMI acute myocardial infarction

found to be 1 per cent,[4, 5] and a very similar figure (0 9 per cent) was encountered among ambulatory patients attending a cardiological center[12] Our figure of 0 17 per cent reflects, as expected, a markedly lower (five fold) prevalence among middle aged working males than among symptomatic patients No comparable data exist

As to the increasing incidence of IVCD with age our data also confirm this tendency The average age of all 123 patients with IVCD was almost 4 years higher than that of the population examined (53 5 against 49 8 years) ($p < 0 01$) and when analyzed according to age groups there is a marked increase of frequency of all types of IVCD with age (Table II) A plateau seems to be reached, however, around the age of 60

The *relative frequency* of our various IVCD types appear to be, in declining order LAH, RBBB, RBBB + LAH and LBBB (TABLE I) It is generally believed that RBBB is much more frequent than LBBB especially in asymptomatic populations Thus, in some studies RBBB has been found to be three to 13 times more frequent than LBBB[1, 3] This is confirmed in the present study, where RBBB is 5 5 times more frequent than LBBB (28 against 5 per cent) However, among hospital patients LBBB appears as frequently or even more frequently than RBBB[37, 38] Obviously the relative frequency of different IVCD is linked to the type of population examined To our knowledge the only comparable study in which the prevalence of all four types of IVCD was examined in the *same population* is that of Rosenbaum and associates[12] who found a similar order of frequency (Table III) except for a total prevalence of IVCD four times higher than ours (9 69 per cent against 2 36 per cent) This may be easily explained by the difference in the population studied (symptomatic subjects versus 'healthy' adults) It is interesting however, that the distribution of the various IVCD remains similar in both studies

As for *sex* preponderance among various IVCD it is interesting that while RBBB appears to be more frequent in men[4, 6, 35, 3] LBBB was found to be equally distributed[34] or even more frequent in women[24, 39] The information concerning LAH is controversial and insufficient, thus while LAD has been claimed to be more frequent in men,[33] LAH has been encountered more frequently in women[39] Our study, as well as that of Yano *and associates*[32] cannot add to the subject since both were confined to males

Etiology

The etiology, clinical implications and long term prognosis of right and left BBB have been extensively commented upon in the literature but the *information* pertinent to LAH or RBBB + LAH is scant The most frequent etiologies involved in IVCD are ischemic and hypertensive heart disease[12, 3, 40, 43] Rarely rheumatic infective, congenital degenerative or traumatic heart disease or the 'cardiomyopathies' are implicated[16, 37, 41, 44] Our group of 123 patients with IVCD was clinically *divided* into three subgroups (1) 35 patients (28 per cent) with ischemic heart disease (IHD) (2) 24 patients (20 per cent) with hypertension (HT) but without IHD and (3) 64 patients (52 per cent) with no evidence of ischemic, hypertensive rheumatic infective, or other heart disease (Table IV)

1 ***Ischemic heart disease and hypertension*** While IHD and HT constitute the most frequent etiologies involved in IVCD their incidence differs in various populations In two early reviews dealing with hospital populations IHD and HT were detected in almost all patients with

Table VI Progression of ECG pattern in 5 patients with HT

Patient no	*Age (years)*	*Initial IVCD*	*Time of appearance (years)*		*Remarks*
			BFB	*CHB*	
1	59	LAH	5	—	—
2	63	RBBB	2	—	—
3	64	RBBB	10	—	—
4	59	RBBB	4	4	Pacemaker insertion
5	52	RBBB	Not documented	9	Pacemaker insertion

BBB and their prognosis was found to be poor accordingly [0,41] Later studies on young and healthy aircraft personnel often failed to reveal any signs of heart disease in many subjects with IVCD and their prognosis was thus obviously much better

However if various types of IVCD are considered within a defined population there appear to exist differences between the roles played by the ischemic etiology in each type of IVCD Thus in our material IHD was present in five of six patients with LBBB but in only seven of 34 (21 per cent) of patients with RBBB (p 0 01) Moreover even if HT is considered along with IHD these etiologies together are involved in less than half (44 per cent) the cases of RBBB (Table III) Likewise in a younger and selectively healthy population the proportion of IHD and HT was found to be as low as 5 per cent among patients with RBBB as against 16 per cent in LBBB Indeed most reports favor a closer relationship between IHD with left than with right BBB

The relationship of LAH to IHD was similar in our study to that of RBBB Thus 28 and 19 per cent of patients with LAH had IHD or HT respectively when considered together practially half (47 per cent) these patients were linked with these etiologies (Table IV) Very little information is available in the literature on the clinical etiology of LAH Thus we are aware of only two relevant studies excluding those dealing with simple LAD one revealing 71 per cent of IHD and/or HT among 128 symptomatic patients with LAH the other disclosing 33 per cent of these etiologies among 119 asymptomatic adult males [3] The latter figure is quite lower than ours (33 versus 47 per cent) in spite of the similarities in the types of population studied for which we have no explanation

As for RBBB + LAH here also our figures are similar to those of isolated RBBB or LAH groups Thus two and two out of nine patients had IHD or HT respectively when considered together practically half the cases (four out of nine) were linked with these etiologies (Table IV) Similar figures emerged in the study of Rosenbaum and colleagues [2] concerning 140 patients with RBBB + LAH 28 per cent of whom had IHD and 48 per cent either IHD or HT In a few series of hospital patients the proportion of IHD among subjects with RBBB + LAH was obviously higher varying from 36 to 73 per cent [7]

In contrast to the above mentioned investigations in which different populations are compared the advantage of our study resides in its ability to compare the role played by IHD or HT among various IVCD in the *same* segment of populations This reveals interestingly that except for LBBB in which the incidence of IHD is significantly higher the role played by IHD and/or HT is practically the same in all other three types of IVCD suggesting a similar etiology for these three types

It can be speculated that silent coronary disease may be present in some adult males with IVCD and without clinical IHD Indeed angiographic studies have shown coronary narrowing among some patients with RBBB [3] and in a higher proportion among those with LBBB [3] While to the best of our knowledge angiocardiographic studies have not been performed in patients with LAH or RBBB + LAH the similar frequency of clinical IHD among the latter and the RBBB group in our study suggests silent coronary disease as a cause for LAH or RBBB + LAH as well

2 Rheumatic and infective heart disease

Valvular heart disease is often mentioned when dealing with the etiology of IVCD and has been claimed to be involved in 3 to 10 per cent of cases of BBB [3,38] [3] In the series of Rosenbaum and associates [2] a rheumatic aortic lesion was found

often than not an isolated disease of the conduction system affecting mainly both bundle branches Although it seems self evident that this process may produce isolated BBB as well as CHB and although Mahaim [4] as early as in 1931 wrote that BBB and CHB may constitute two facets of the same condition degenerative disease is rarely mentioned as a cause for isolated BBB Furthermore Lev and Bharati[9] claimed in 1975 that while an idiopathic etiology certainly exists for CHB and probably for RBBB + LAD this is doubtful for isolated BBB It is therefore interesting that our material strongly suggests a degenerative etiology for some cases of MFB although on clinical grounds only Obviously it is impossible to point out which patient with MFB suffers from degenerative disease of the conduction system (DDCS) unless serial ECG s showing progression are available Such progressive changes were observed in 5 of our patients of Group 3 (i e without IHD or HT) and were therefore considered to represent examples of a DDCS (see later) More of our patients may have had the same etiology the slow progression of their IVCD preventing a definite diagnosis during the study

To summarize while it is impossible on clinical grounds alone to assess the exact etiology of the IVCD in each case it appears from our material that about one third of subjects with IVCD are associated with IHD and one fifth with HT (35 and 24 of 123 respectively) Among the remaining 64 a few may constitute examples of silent coronary disease or of a state after myocarditis while at least 4 per cent (five of 123) may be ascribed to a DDCS

Progression

Progression of conduction disturbances occurred in 15 patients all belonging to the RBBB or LAH groups thus constituting 14 per cent of 108 patients with monofascicular blocks (MFB) Progression was displayed by the appearance of an added fascicular block or CHB (Table V) P R prolongation as a single feature was not encountered None of the nine patients with RBBB + LAH showed further progression and likewise no progression was recorded among the six patients with LBBB (four of whom died during the follow up) Progression of IVCD is discussed separately from the ECG and etiologic point of view (Tables V and VI)

Table VIII Comparison between 1 658 outpatients (Rosenbaum et al[1]) and 5 204 Israeli working males prevalence and distribution of IVCD

Type of IVCD	*No of patients*		*Prevalence in population (per cent)*	
	Rosenbaum et al	*Ours*	*Rosenbaum et al*	*Ours*
LAH	6 (47 %)	74 (60 %)	4.58	1 42
RBBB	53 (33%)	34 (28%)	3 19	0 65
RBBB + LAH	15 (9%)	9 (7%)	1 02	0 17
LBBB	17 (11%)	6 (5%)	0 90	0.12
TOTAL	161 (100%)	123 (100%)	9 69	2 36

1 Progression of ECG pattern The interrelation between BFB and CHB has been confirmed both by retrospective and prospective studies while the interrelation between MFB and higher degrees of IVCD has received little attention so far While some retrospective studies mention the type of MFB preceding the occurrence of BFB or CHB very few prospective studies of MFB progression have been published Thus Bhat and associates[19] who followed 455 patients above the age of 65 with various IVCD for an average period of 2 years found no progression Rotman and Triebwasser who followed 394 subjects with RBBB (average age 36 years) for more than 10 years found that only one (0 25 per cent) developed CHB In contrast we found a 22 5 per cent progression among our patients with RBBB (eight of 34 Table V) These conflicting findings may be explained by the short follow up period in Bhat and colleagues study and the younger age of the subjects followed by Rotman and Triebwasser As for LAH to the best of our knowledge no prospective study dealing with this form of IVCD is available In our material 9 5 per cent of LAH progressed within the 10 year follow up (seven of 74 Table V) Thus our data demonstrate that MFB progress in a significant proportion of cases (15 of 108 14 per cent) if followed long enough Among these 15 patients 10 progressed to bifascicular block (BFB) or BBBB only three displayed first BFB and then CHB and the remaining two progressed to CHB without documented BFB (Table V) This suggests as expected that in addition to BFB MFB is an important precursor of CHB Interestingly the

Table VII Progression of ECG pattern in 5 patients with IVCD of degenerative origin

Patient no	*Age (years)*	*Initial IVCD*	*Time of appearance (years)*		*Remarks*
			BFB	*CHB*	
1	50	LAH	5	8	Pacemaker insertion
2	54	LAH	10	–	–
3	44	LAH	10	–	–
4	46	RBBB	5	–	–
5	54	RBBB	10	–	–

in 7 8 and 7 7 per cent of subjects with LAH and RBBB + LAH, respectively None of our patients had evidence of rheumatic valvular disease, which may be attributed to differences in the type of populations studied (symptomatic subjects versus "healthy' adults)

In every large series of BBB some are ascribed to infective or viral 'myocarditis ' Thus in the material of Rosenbaum and colleagues,[1] Chagasic myocarditis was implicated in 9 3 and 27 8 per cent of cases with LAH and RBBB + LAH, respectively Likewise, Rotman and associates [3] could obtain a history of prolonged ' flu like ' illness shortly before the appearance of BBB in the majority' of their patients The possibility of silent myocarditis as a cause of IVCD is supported by the presence of a mild diffuse abnormality of the ventricular myocardium in patients with acquired BBB [45, 46] It is of course conceivable that some of our asymptomatic non progressing IVCD patients suffered from an episode of silent myocarditis in the past although a suggestive history was not obtained in any

3 **Congenital anomaly** It is also possible that some IVCD discovered routinely may be congenital in nature If this was true however they should have been occasionally recorded among otherwise healthy infants and children With regard to RBBB it should be recalled that while secondary R waves in right chest leads have been reported in up to 98 per cent of normal children,[47] and that a pattern of RBBB is thus frequently considered a "normal variant' in this age group Ziegler[48] diagnosed complete RBBB in only 6 5 per cent of normal infants according to the form of ventricular deflection in precordial leads Furthermore, others claim that an organic impairment of the right bundle is very rare in normal children and deserved special notice [49, 51] Our impression from reviewing the literature is that an isolated congenital block of the right bundle in children, although possible, is rare On the other hand the frequency of LBBB or LAH in infants may be assessed more accurately because of better criteria LBBB is extremely rare in normal infants [3, 7, 5, 53] and seen only in unusual forms of congenital heart disease Even in young adults, as mentioned this form of IVCD is seldom encountered [7, 9] and it is possible to disclose an organic basis for most cases of LBBB in older age groups Therefore a congenital etiology cannot be invoked in most cases of LBBB [23] As for LAH, although it is the most common IVCD in adults tables showing the range and mean axis of the ECG of infants and children from birth up the age of 16 show a constant leftward tendency with age but not to the left of –20 degrees [49, 5, 53] Among 1 500 aviators aged 18 to 32 no severe LAD was found [11, 3] Moller and colleagues[54] described six normal children with LAD but not to the left of –45 degrees [54] and the only exception to these reports is the above mentioned finding among Navajo children [36] Thus it seems that like LBBB LAH and RBBB + LAH are quite rare in childhood. It should also be added here that although a familial tendency to a conduction disease has been recently reported [55] this was observed only in adult relatives of patients with IVCD It can be concluded from the above that the great majority of IVCD are acquired in origin except when associated with a congenital heart lesion

4 **Degenerative disease** A degenerative etiology for conduction disturbances was considered by Mahaim[56] and by Yater and colleagues[57] already in the early 1930s [56, 57] but studied in detail only 30 years later by Lev, Lenegre and others [1, 2, 3, 60] The latter termed the lesion as a sclerodegenerative process sclerosis of the left side of the heart skeleton ' [59] or primary idiopathic heart block [60] In laborious histological studies they showed that chronic CHB is more

IVCD in this group was rapid and the mortality rate very high. Thus, all four patients who reached the stage of BFB or BBBB did so within the first 5 years and the two who reached the stage of CHB died despite pacemaker insertion (Table VI). It seems that in this group the natural history of IVCD parallels the natural history of IHD in general.

In the second group (HT) a different pattern emerges. Even though the rate of progression appears to be similar to the previous one (Table VIII) its long term prognosis seems better. Thus, while here also two of five patients reached the stage of CHB requiring pacemaker insertion, all were alive and well at the end of 10 years.

In the third group (without IHD or HT) the five patients with progressive IVCD (Table IX) most probably represent true instances of progressive degenerative disease of the conduction system (Lenegre's or Lev's disease) and may well illustrate the natural history of this condition. Indeed, in contrast with previous studies, our patients constitute a homogenous group well separated from the ones with IHD and HT and followed for 10 years. In these patients the rate of progression of IVCD seems the slowest (Table IX) and its long term prognosis favorable. Thus, all five patients were alive and well at the end of 10 years including the one with pacemaker insertion.

Furthermore, while lack of information as to the appearance time of the initial IVCD precludes any comment on the length of the degenerative process, it can be safely speculated that more examples of DDCS as yet unmasked are included among the 64 patients of this group. Indeed, CHB has been reported to occur as long as 23 years after BFB.[4] As to the evolution of the ECG pattern in this disease, it should be noted that while the initial tracings showed LAH in three and RBBB in two patients and that all five progressed to RBBB + LAH during the study, LBBB was not encountered at any time in this group. In this respect Lenegre[3] already observed that among his cases progressing conduction disturbances began mostly as RBBB. Whiberg and associates noted that none of the uncomplicated LBBB progressed to CHB during a 3 year follow up period while some of the RBBB + LAH did. Among Rotman and Triebwasser's[2] 125 young LBBB patients only one developed CHB and this was linked to an attack of acute myocardial infarction. The above suggests that while LBBB may often constitute a link in the progression of IVCD to CHB in IHD,[33, 6, 61] this pattern is an infrequent manifestation of DDCS. To summarize, the frequency of DDCS appears to be at least 0.1 per cent (five of 5,204) among a population of the type studied here, or 4 per cent of all types of IVCD (five of 123). It is likely to begin with an ECG pattern of RBBB or LAH in middle age or earlier and to progress to BFB and later to CHB within a few years or a few decades. LBBB does not seem to be a frequent manifestation of this disease. Its prognosis is favorable, life expectancy remaining unaffected, especially since the advent of pacemaker therapy.

Summary

The ECG tracings of 5,204 working males aged 40 years and over, representing a random sample of Israeli civil service employees, were reviewed and 123 (2.36 per cent) displaying intraventricular conduction disturbances (IVCD) in the form of left anterior hemiblock (LAH), RBBB, RBBB + LAH and LBBB were followed for a period of 10 years (1963 to 1973). While these patients were slightly older than the population they were derived from (53.5 versus 49.8 years average age), there was no significant difference in ages between the various types of IVCD but there was a marked increase in the frequency of all IVCD with age. Left anterior hemiblock constituted the most frequent IVCD (1.42 per cent), being twice as frequent as RBBB (0.65 per cent). The prevalence of RBBB + LAH was 0.17 per cent (7 per cent of all IVCD). To the best of our knowledge this is the first time that the frequency of this condition has been assessed in an unselected male population.

The vast majority of these ECG changes seem to be acquired. Ischemic heart disease (IHD) constituted the most frequent associated condition for all types of IVCD (28 per cent), its prevalence being similar (21 to 28 per cent) in LAH, RBBB and RBBB + LAH but much higher in patients with LBBB (five of six patients). Hypertension (HT) not associated with IHD was present in 24 patients and constituted the next most frequent factor (20 per cent). No definite etiology could be demonstrated in the remaining 64 patients (52 per cent) except for five (4 per cent of all IVCD and 0.1 per cent of the

Table IX Associated conditions in 123 patients with IVCD

Type of IVCD	*No of patients*	*Associated clinical condition (No of patients)*			
		*IHD**	*HT**	*Both*	*None*
LAH	74	21 (28%)	14 (19%)	35 (47%)	39 (53%)
RBBB	34	7 (21%)	8 (24%)	15 (44%)	19 (56%)
RBBB + LAH	9	2 (†)	2 (†)	4 (†)	5 (†)
LBBB	6	5 (†)	–	5 (†)	1 (†)
Total	123	35 (28%)	24 (20%)	59 (48%)	64 (5[illegible]%)
Average age (years)	53 5	55 8	55 8	55 8	51 3

IHD ischemic heart disease HT hypertension
†Figures too small for per cent evaluation

number of progressing cases was higher among the group with RBBB (eight of 34, 22 5 per cent) than with LAH (seven of 74 9 5 per cent) ($p < 0\ 05$) This accords with retrospective studies in which a pattern of RBBB was more frequent than LAH in sinus conducted beats of patients with CHB[6] It also accords with Lenegre s observations that RBBB precedes LAH in cases with progressing IVCD It follows that a pattern of RBBB in the adult may not be as innocent as suggested by studies on younger age groups

As stated the inter relationships between BFB and CHB has been confirmed both by retrospective and prospective studies Thus RBBB + LAH has been encountered in 34 to 60 per cent of previous ECG recordings or in sinus conducted beats of patients with established CHB[4,6] Among patients with RBBB + LAH studied from hospital records high degree A V block has been found in six to 28 per cent within an average follow up period up to 3 1 years[4,7,1] Truly prospective follow up studies on this subject have been few and conducted only recently They revealed a 2 7 to 6 0 per cent progression to CHB per average year of follow up[5,6,67]

In our material the pattern of BFB (RBBB + LAH) could be divided in two (a) Nine patients displaying this pattern from the beginning without further change throughout the study (the static type), and (b) Thirteen patients starting with RBBB or LAH (MFB) and developing RBBB + LAH (BFB) during the study, with among these, three showing further progression to CHB (the 'dynamic type) The lack of progression of IVCD observed in the static type is puzzling while the ratio of progression in the dynamic group (three out of 13 reaching CHB) is within the range of the above mentioned reports But when comparing our data with others the following should be noted first, ours is the only general population study, all others being derived from hospital records, then, our follow up period is twice as long as the longest in the literature (10 versus 4 8 years) and last, but most important it is misleading to analyze the natural history of IVCD without considering their etiologies since the latter may actually determine their rate of progression Thus the stability of the static group could tentatively be ascribed to different etiologies, accordingly and in contrast to previous reports we have further analyzed the IVCD progression according to etiology as follows

2 Progression and prognosis and IVCD according to etiology Progression of IVCD occurred in five of our 35 patients with IHD (14 per cent) in five of 24 with HT (21 per cent) and in five of the remaining 64 (8 per cent) Despite these small numbers a different natural history seems to emerge for each group

As far as the group with IHD is concerned the progression of IVCD could very well represent progressing peri infarction or intraparietal blocks secondary to IHD rather than intrinsic disease of the conduction system Indeed four of these patients had sustained one or more episodes of acute myocardial infarction before or during the study, and the fifth suffered from anginal syndrome (Table VII) Furthermore in our material the only two instances of BBBB a pattern which usually indicates extensive myocardial damage with intraparietal block ** were encountered in this group (patients Nos 2 and 3 Table VII) With regard to prognosis the progression of

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population studied) who displayed progressive IVCD and were considered to represent examples of a degenerative disease of the conduction system (DDCS) The latter confirms that mono fascicular blocks (MFB) may represent an initial stage of DDCS

From the ECG point of view, 14 per cent of cases with MFB showed progression to bifascicu lar block (BFB) or complete heart block (CHB) within 10 years, regardless of etiology This was more frequent in RBBB than in LAH (22 5 per cent versus 9 5 per cent) From the clinical point of view, the natural history of IVCD in patients with IHD parallels the natural history and prog nosis of this disease In contrast, the prognosis of IVCD in patients with isolated HT or in asymp tomatic subjects, was more benign even in patients reaching the stage of CHB The natural history of DDCS began as RBBB or LAH in middle age or earlier and progressed to CHB through the stage of BFB This process may last from a few years to a few decades, LBBB seems to be rarely if ever encountered in its course

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Serum myoglobin in acute myocardial infarction A clinical study and review of the literature

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The diagnosis of acute myocardial infarction (AMI) is made conventionally on the basis of the clinical history, serial electrocardiograms and serum enzyme changes This approach suffices in the majority of instances However recent enthusiasm for early intervention to reduce infarct size and the attempt to optimize coronary care utilization on a cost effective basis has raised the need for early, sensitive, and specific indicators of myocardial necrosis

Recent reports have suggested that elevations of serum myoglobin (SMb) might provide such a parameter and permit estimation of prognosis and infarct size [1-3] However a recent editorial has questioned the value of SMb in assessing suspected myocardial injury [4]

We report here a study of serum myoglobin in a consecutive series of patients with suspected acute myocardial infarction (AMI), and in several other noncardiac conditions The sensitivity specificity and practical value of SMb are discussed in relation to a review of the literature

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Received for publication Mar 31 1978

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Table I A rating system for suspicion of acute myocardial infarction (AMI)*

	Points		
Criteria	*0*	*1*	*2*
Chest pain	None	Atypical	Typical pain
ECG changes	No changes	Non specific ST T changes	New Q waves evolutionary ST T changes
Enzyme changes	None	Transient slight elevation	Sequential rise and fall of levels

*Interpretation 5 to 6 points = Definite AMI < 5 points = No definite AMI

Materials and methods

Sixty consecutive patients admitted to an intensive care unit with the initial diagnosis of possible AMI were studied The diagnosis of AMI was established by a rating scale including chest pain ECG changes and enzyme elevations (Table I) Each case was evaluated for acute myocardial infarction by two independent observers without prior knowledge of the myoglobin data Patients with 5 to 6 points on this rating scale were judged to have a definite AMI (Group 1) and the others were classified as having no definite MI (Group 2)

In all cases, the information which was recorded included age sex previous history of AMI angina heart failure valvular disease renal

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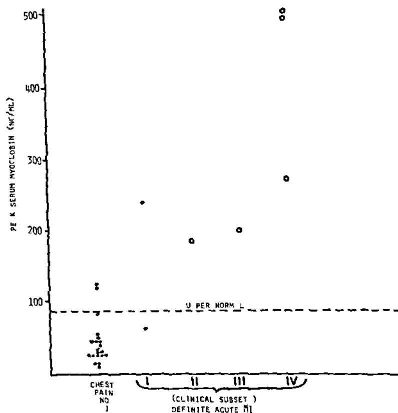


Fig 1 Serum myoglobin in acute myocardial infarction ● = alive at two weeks ○ = dead at two weeks * see *Table II*

Table II. Definition of clinical subsets in acute myocardial infarction*

Subset	*Pulmonary† congestion*	*Peripheral†† hypoperfusion*
I	−	−
II	+	−
III	−	+
IV	+	+

After Forrester et al
††See text for lin c l nteria

Table III. Profile of patients studied

Group	*Points*	*Number of cases*		*%*	*Sex*	*Age ± S.D*
No definite AMI	1	10	38	63%	22 M 16 F	63 34 ± 14 27
	2	19				
	3	5				
	4	4				
Definite AMI	5	9	22	37%	14 M 8 F	63 41 ± 12 71
	6	13				

See T ble I

disease diabetes mellitus liver disease peripheral vascular insufficiency alcohol abuse or seizure disorder There was also elicited information regarding recent history of unusual physical exertion musculoskeletal trauma seizures intramuscular injections alcohol or drug intake Careful inquiry was made as to the exact time of onset of the present episode of chest pain or discomfort Complete physical examination was recorded with special attention to evidence of hypoperfusion (oliguria altered mentation skin changes low BP or tachycardia) pulmonary congestion (rales tachypnea abnormal chest x ray) presence of musculoskeletal trauma or peripheral vascular disease Clinical and hemodynamic subsets were assigned according to the classification of Forrester[5] (Table II) All patients were evaluated and managed by a standard coronary care protocol which included serial enzymes and electrocardiograms and conventional blood chemistry Intramuscular Demerol (meperidine)

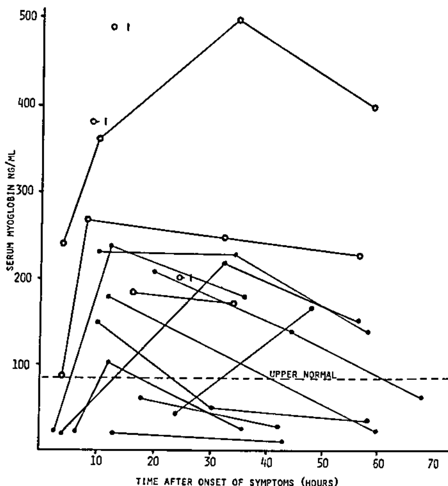


Fig 2 Relationship of myoglobin levels to onset symptoms in acute myocardial infarction ● = alive at two weeks ○ = dead at two weeks ○–I = died shortly after sample collection

was used for sedation and analgesia and morphine for refractory pain Patients in clinical subsets III and IV (i e with clinical evidence of hypoperfusion) had Swan Ganz catheterization for measurement of pulmonary arterial wedge pressure Management with diuretics, inotropic drugs fluids vasodilators and other agents followed accepted principles[5] A record was kept of the number, route, type and time sequence of administration of all medications Details of cardiopulmonary resuscitations, defibrillation and other procedures were recorded

Patients with various other conditions were also studied including pre and postoperative non cardiac surgery (Group 3), critically ill patients in the intensive care unit without myocardial disease (Group 4), patients receiving multiple intramuscular injections (Group 5), and patients with heat stroke (Group 6)

In Groups 1 and 2 (acute or suspected myocardial infarction), samples were drawn by venipuncture upon admission (Day 1) and on Days 2 and 4 simultaneously with other conventional serial studies In those cases where the time of onset of symptoms was reasonably certain (92 per cent of cases), the number of hours from onset was noted with each sample Samples in the other groups were drawn at appropriate times All samples were frozen at –20° C for analysis in batches

Serum myoglobin was determined by radioimmunoassay employing I^{125} labelled myoglobin* based on the method of Stone and colleagues[1] The assay was reproducible, sensitive, and specific The normal value for serum myoglobin was 31 ± 25 ng /ml A value of 85 ng /ml is considered the extreme upper limit of normal

All information was coded and analyzed

Results

The profile of the population studied for possible AMI is indicated in Table III Thirty three per cent of patients (22 of 60) had definite AMI (Group 1) and 63 per cent (38 of 60) (Group 2) had equivocal or negative criteria The two groups were comparable by age and sex distribution

*From Nuclear Medicine Systems Inc Newport Beach Cal 9?663

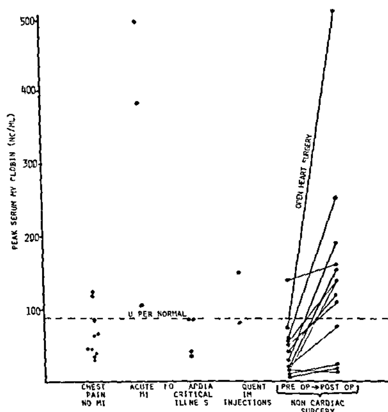


Fig 3 Myoglobin levels in other conditions studied

Fig 1 shows actual myoglobin levels in the two groups Values were significantly elevated in the group with acute myocardial infarction (172 ± 124.9 ng/ml) ($p < 0.001$) There was a significant correlation of higher peak SMb values with higher clinical subsets As expected the immediate mortality rate (two weeks) was significantly lower in subsets I and II as compared with III and IV ($p < 0.01$) (Fig 1)

Three patients with AMI failed to show significant elevations of SMb All were in clinical subset I and had mild transient elevations of SGOT

The exact time of onset of symptoms was known in 92 per cent of cases Fig 2 demonstrates SMb values as a function of total duration from the onset Typically elevations were noted at 6 to 8 hours. Early peaks were noted in two patients (less than 2 hours) and both died Sustained elevation of SMb into the third day was associated with increased mortality ($p < 0.1$)

Twenty one per cent of patients without definite evidence for AMI (1 to 4 points on the rating scale) showed peak myoglobin levels elevated above normal There was no trend towards higher values in those patients with higher point ratings Four of these patients had possibly alternative explanations for the rise in SMb (chronic renal failure 3 trauma 1) One patient had a final diagnosis of pericarditis secondary to a post myocardial infarction syndrome

Fig 3 shows SMb values in the other groups of patients studied Significant elevations were seen in postoperative (non cardiac) states (58 per cent) heat stroke (100 per cent) critically ill patients in the intensive care unit without cardiac disease (27 per cent) and 50 per cent of those patients receiving frequent IM injections

Discussion

Myoglobin is a low molecular weight heme protein synthesized and found exclusively in skeletal and cardiac muscle and is immunochemically identical from the two sources[6] Damage to either of these tissues would theorectically elevate serum myoglobin levels Renal clearance is rapid though variable and hence myoglobinemia following a single injury tends to be transient

Significant myoglobinuria following AMI has

Table IV Reported studies of myoglobinemia in myocardial infarction

Reference	Assay technique	Normal values of SMb (ng/ml)*	Patient selection method
Kagen et al 1975[7]	Complement fixation assay	Not detectable	Admissions to CCU†
Jutzy et al 1975 Abstract	Radio immunoassay (RIA)	20 9 ± 23 3	CCU admissions
Stone et al 1975[3]	RIA	6 85	CCU admissions (consecutive ?)
Stuart et al 1975[1] Abstract	RIA	Not detectable	Not specified
Klocke et al 1976[1] Abstract	RIA	25 ± 23 (5 75)	CCU admissions
Stone et al 1977	RIA	31 ± 1 3 (SE) 6-85	CCU admissions
Kollman et al 1977[13] Abstract	RIA	NS < 75	Consecutive CCU admissions
Gilkeson et al 1978	RIA	6 85	Patients with chest pain in Emergency room
Reichlin et al 1978	RIA	25 ± 23	Admissions to CCU†
Present study	RIA	< 85	Consecutive CCU admissions

Smb = Serum myoglobin values in ng/ml ±1 S D
†CCU = coronary care unit.
‡NS = not specified
§AMI = acute myocardial infarction

been reported in several studies[7 11] However urine myoglobin levels showed extreme variability with regard to the time course of excretion and are poorly correlated with peak serum levels and severity of infarction

Myoglobinemia following AMI was first reported by Kagen and colleagues[2] utilizing a complement-fixation assay which would detect up to 30 ng/ml of SMb Elevated levels over a wide range were demonstrated in 11 of 21 patients with conventional evidence of myocardial necrosis Higher values tended to correlate with both increased severity of infarction and greater mortality However the assay technique tended to underestimate small quantities of myoglobin because of serum interference and normal persons had undetectable levels

A sensitive, specific, and accurate radioimmunoassay for SMb was first reported by Stone and co workers[1] Currently accepted normal values for SMb are 31 ± 50 (2SD) ng/ml, based on 135 normal subjects studied by this group The highest value found in this population was 85 ng/ml and this was considered the upper limit of normal' Normal subjects studied by other groups showed similar results, with maximum values ranging from 75 to 85 ng/ml[3 13]

The available information on myoglobinemia following AMI in the English language literature is summarized in Table IV Two factors make comparison of these studies difficult First with one exception[13] none of the reports indicate whether the patient populations studied constituted random samples consecutive series or selected groups with suspected AMI Secondly while most studies analyzed the SMb values in

Sample collection		*Serum myoglobin values*				
		Acute myocardial infarctions			*Chest pain no AMI§*	
Timing	*Relationship to onset of symptoms*	*SMb*	*Elevated in*	*Peak values (hrs)*	*SMb*	*Elevated in*
On admission (5)-serial	NS‡	300 3700	11/21 (52%)	?	Not Detectable	0/12 (0%)
QIH × 6hrs Q3H × 12hrs Q?HH × 3days	Discussed in relation to onset of symptoms	216 6800	30/30 (100%)	9 12hrs from onset	2 88	0/?0 (0%)
Variable serial in 9 patients	NS	380 ± 53 195 ± 47	18/20 (90%)	8-12hrs from admission	41 ± 6	1/?1 (4 8%)
QIH × 12hrs ?4hrs–from 48hrs onset	NS	46-200	5/5 (100%)	7 10hrs from onset	Not detectable	0/2 (0%)
Not specified (frequent)	NS	1390 ± 1350	31/31 (100%)	Early	16? ± 52	8/18 (44%)
Variable (some serially)	NS Related to admission	528 ± 76	62/64 (96 8%)	4 hrs from admission	44 ± 6 0	2/44 (4 5%)
Not specified	NS Related to admission	> 100	8/9 (88%)	?	> 75	0/13 (0%)
On admission	NS	–	5/13 (38%)	–	33 8 (Mean)	2/53 (3 8%)
6-8hrs.	NS	–	9/12 (75%)	–		
Not specified	NS	1368 ± 1357	3?/3? (100%)	–	16? ± 52(8) 38 ± 16(11)	8/19 (42%)
On admission Day 2 & Day 3 (A M)	Discussed in relation to onset of symptoms	172 ± 124	19/2? (86%)	6-8hrs. from onset	63 6 ± 62 38	8/38 (21%)

relation to the time elapsed after admission to the hospital a few (including the present one) attempted to relate the timing of sample collec tion to the onset of the symptoms of AMI The duration of significant myoglobinemia was brief in most studies and return to normal values often occurred in less than 24 hours Hence although the exact time of onset of symptoms is difficult to determine in some patients correlation with the duration of symptoms is probably more valid than with duration of hospitalization In the present study it was possible to determine the time of onset of chest pain in 92 per cent of the cases

In most studies myoglobinemia was detected as early as four hours after admission and often preceded the appearance of elevated levels of CPK and the CPK MB fraction The value of such early detection is questionable First confirming the diagnosis a few hours earlier is unlikely to alter the basic management of a case of AMI On the other hand the absence of significant elevation of SMb alone would not be sufficient to abandon intensive coronary care if there is any other evidence suggesting an AMI Secondly in most laboratories RIA procedures are usually carried out in batches on stored samples for reasons of practicality and economy To perform the assay on a single sample as an emergency procedure would not be cost effective except under unusual circumstances A practical approach would be to collect and store sam ples for SMb assay to be done only in those cases in which conventional parameters are equiv ocal

Significant elevations in SMb were noted in the large majority of cases of AMI in various series (Table IV) With increased frequency of sam pling 100 per cent of cases showed myoglobin emia [11, 15] However these studies used hourly

Table V Conditions in which elevated serum myoglobin levels have been reported

1	Acute MI (See Table IV)
2	Angina without infarction (See Table IV)
3	Rhabdomyolysis
4	Multiple fractures * Muscle trauma *
5	Acute vascular occlusion?
6	Renal failure *
7	Myopathies type not specified
8	Vigorous exercise
9	I M injections
10	Open heart surgery* *
11	Non cardiac surgery
12	Grand mal seizures
13	? Dig toxicity
14	Ventricular tachycardia
15	Widespread cancer
16	Pericarditis ?*
17	Circulatory shock *
19	Excessive alcohol ingestion?

Present study

Table VI Conditions in which elevated serum myoglobin levels were not found

1	Angina without infarction (See Table IV)
2	Congestive heart failure without AMI *
3	Cardiac cath *
4	Bicycle stress testing*
5	Moderate exercise
6	I M injections (5 subjects–10 c c saline injections)
7	Liver disease
8	Scleroderma *
9	Rheumatoid arthritis
10	Thryotoxicosis *
11	Diabetic ketoacidosis
12	Pancreatitis

sampling for SMb, which is neither practical nor desirable in practice In the present study, a *deliberate* attempt was made to evaluate the usefulness of a restricted number of samples obtained at the same time as other routine studies Even with such infrequent, sampling, 86 per cent of cases of definite AMI showed significant elevations of SMb It would appear that more frequent samples might be of value in individual cases where clinical suspicion of myocardial necrosis is high but other parameters are equivocal It must be pointed out that Kagen and associates [16] in an early study, suggested that there appeared to be a staccato phenomenon' with considerable variation in the levels of SMb in the early hours following infarction

In the present study only three patients with definite evidence of AMI failed to show elevations of SMb These three all in clinical subset I showed only mild transient elevations of cardiac enzymes In one patient, sampling time (3 and 44 hours after onset of symptoms) may have missed a transient myoglobin peak In the two others modest evolutionary changes of SMb within the normal range were seen However there is no data available on day to day variations of SMb in normal individuals and hence no significance can be attributed to this

Peak values for SMb in AMI were reported to occur in a varying period ranging from 4 to 12 hours after admission to 6 to 12 hours after onset of symptoms in various series (Table IV) Actual values also showed a considerable range, a few with levels as high as 3 000 to 6 000 ng/ml Several studies attempted to correlate the peak myoglobin level with the severity and prognosis of the infarction Significantly higher levels were noted in patients who also had congestive heart failure [1, 2] In the present series a significant correlation was noted between the height of the myoglobin peak and the severity of the infarction as defined by the clinical subsets of Forrester and co workers [5] However it must be noted that patients in subsets III and IV had renal hypoperfusion by definition, and hence might have had decreased clearance of myoglobin It has also been suggested that severity of myoglobinemia might be used to estimate infarct size [1] In studies on experimentally induced AMI in dogs, such correlation was possible [17] However the transient and unpredictable nature of the myoglobin peak and the possible 'staccato phenomenon' alluded to above make it unlikely that SMb can be more reliable than currently available techniques for mapping infarct size

The incidence of elevated SMb in patients with chest pain, but no definite AMI varies greatly, from 0 to 44 per cent in various series (Table IV) This may relate in part to variations in the diagnostic criteria for an AMI Further, several other conditions are now known to produce elevations in SMb (see Table V) In the present study 21 per cent of patients (8 of 38) with chest pain but no definite evidence of AMI showed elevated SMb levels Of these three patients had chronic renal failure and one had sustained musculoskeletal trauma before admission One other patient was diagnosed as having a pericarditis probably secondary to a post myocardial infarction syn

drome In the other three no apparent explanation was found It is possible that some of these patients may have had a small infarction which could not be detected by conventional methods However there was no trend towards increasing myoglobin levels with increasing suspicion (higher point count) of AMI

Although SMb elevations are very sensitive for AMI they are certainly not specific Table V lists the conditions in which elevated myoglobin levels were found by various workers In the present study 58 per cent of postoperative (noncardiac) patients 50 per cent of patients receiving frequent IM injections and 27 per cent of patients admitted to an intensive care unit for critical noncardiac illnesses showed significant elevations of SMb (Fig 3) Open heart surgery resulted in very high levels of SMb[1, 12] Other conditions in which myoglobinemia has been reported include extensive trauma rhabdomyolysis acute vascular occlusion of an extremity grand mal seizures metastatic cancer and following ventricular tachycardia without definite evidence of myocardial infarction (Table V) Because myoglobin is normally cleared rapidly by the kidney SMb values are difficult to interpret in the presence of acute or chronic renal failure There is no data available at the present time which allows correlation of the severity of the renal failure with the degree of elevation of the SMb While myoglobinuria by itself is well known to be associated with renal failure the quantities released in AMI are not significant in this regard

While rigorous exercise is well known to cause significant rhabdomyolysis bicycle stress testing and moderate exercise did not appear to raise the SMb[5]

While Stuart and associates[5] found that five subjects given 10 c c saline injections did not show elevated SMb other studies including the present indicate that patients receiving frequent deep IM injections can have significant myoglobinemia[14] Stone and colleagues found that cardiac catheterization did not alter myoglobin levels

It is evident that many factors some of them rather non specific can alter myoglobin levels The SMb in myocardial infarction should therefore be interpreted only in light of other associated conditions

The transient and dramatic nature of the myoglobin peak suggests that a distinct second peak might be of value in making the diagnosis of an early recurrent AMI or extension of infarction in the situation where other conventional parameters are still abnormal following the first infarction Kollman and co workers[14] have reported such a case In this situation SMb might be distinctly advantageous

Conclusions

The results of this study and a review of the literature permit the following conclusions and suggestions regarding myoglobinemia in acute myocardial infarction

1 Radioimmunoassay of serum myoglobin (SMb) is a sensitive indicator of myocardial damage in the early hours following an acute myocardial infarction (AMI) Even with infrequent sampling more than 85 per cent of patients show significant elevations of SMb Sensitivity is higher with frequent sampling

2 It is suggested that serum for analysis should be collected on admission and daily for two days i e at the same time as other conventional studies are obtained The specimens may be frozen and the assay performed if in retrospect there is significant doubt regarding the diagnosis

3 Careful note should be made of the relationship of the timing of sample collection to the time of onset of chest pain Elevations of SMb may be expected to peak between 4 to 12 hours following the onset of pain

4 Elevations of SMb are nonspecific for AMI It is probably valueless in the presence of renal failure rhabdomyolysis extensive trauma postoperative states (cardiac and noncardiac) acute vascular occlusions of extremities and following seizures It should be interpreted with care following intramuscular injections vigorous exercise ventricular tachycardia, and cardiopulmonary resuscitation Inadequate data is available regarding pericarditis and cardiomyopathies Twenty five per cent of critically ill patients with multiple non cardiac problems have a raised SMb which cannot be adequately explained in all instances

5 At present there is inadequate data to suggest that SMb is superior to any of the conventional methods for assessment of the extent of infarction However very high levels and sustained elevations tend to be associated with a poorer prognosis

6 SMb may be of special value in the diagnosis

of early recurrent AMI or extension of infarction

The authors wish to acknowledge the excellent technical assistance of Elizabeth Smith B S

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Infective endocarditis Part III Prevention of bacterial endocarditis

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While antibiotic therapy of infective endocarditis has dramatically improved patient survival the morbidity and mortality of this infection remains appreciable[1,2] Well controlled clinical studies investigating the effectiveness of antibiotics in preventing the development of infective endocarditis are not available Therefore the present recommendations for antibiotic prophylaxis have been based on extrapolations from several types of data (1) the pathogenesis of infective endocarditis often involves implantation of the causative organism on damaged cardiac valves during transient bacteremia (2) the transient bacteremia often follows particular mechanical procedures[5] (3) the species of organisms isolated during these bacteremias and those which frequently cause endocarditis have relatively predictable antibiotic susceptibilities[6] (4) knowledge of the bactericidal activity and clinical pharmacology of antibiotics suggests prophylactic drug regimens which would be likely to decrease the incidence or intensity of such transient bacteremias and the subsequent multiplication of the pathogen in the nidus on the cardiac valve—a reduction in the incidence of infective endocarditis would therefore be expected (5) the prophylactic drug regimens have been modified after considering the results of studies which have evaluated antibiotic prophylaxis in animal models of endocarditis This paper will review some of the data and the current recommendations for the prevention of endocarditis

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Di ring th course of this t dy Dr Lowy was supported by a training grant (*T01 AI 00405- 07 AID) from th N ti nal Inst tut of Allergy and Infect ous Diseases.

Received for public tio J ne 19 19 8.

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Prevention of rheumatic fever

The use of antibiotics to prevent recurrent episodes of rheumatic fever by preventing recurrent Group A streptococcal throat infections must be distinguished from antimicrobial prophylaxis of bacterial endocarditis These two subjects are often confused and it should be emphasized that antibiotics administered in order to prevent rheumatic fever are not only inadequate as preventive therapy for endocarditis but can alter the antibiotic susceptibility of viridans streptococci which are part of the indigenous mouth flora making endocarditis prophylaxis more difficult However reducing the incidence of rheumatic fever and resulting rheumatic valvular disease potentially reduces the population of patients at risk of developing infective endocarditis

Large scale studies with military recruits have shown a direct relationship between elimination of Group A streptococci from the throat and reduction in the incidence of rheumatic fever[11,12] During epidemics the incidence of rheumatic fever following streptococcal pharyngitis is 3 per cent[2] Treatment within one to two days of infection is 95 per cent effective in reducing the subsequent rheumatic fever attack rate, therapy given one two or even three weeks after an infection will reduce the incidence of rheumatic fever by 90 per cent 67 per cent and 42 per cent respectively[3]

Prophylaxis of recurrent Group A streptococcal throat infections is recommended for patients with a past history of rheumatic fever Sydenham s chorea or rheumatic valvular disease and represents an attempt to prevent the recurrence

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Table I Prevention of rheumatic fever* (Choices listed in order of preference)

Primary prevention—Treatment of Streptococcal Pharyngitis

1. Benzathine penicillin G 1 2 million units IM If the patient weighs less than 60 lbs the dose is 600 000 units IM
2. Oral penicillin G 200 000 units 3 4 times/day for ten days
3. In penicillin allergic patients erythromycin 20 mg /lb /day (up to 1 Gm /day) in divided doses for ten days

Secondary Prevention—Continuous prophylaxis†

1. Benzathine penicillin G 1 2 million units IM every four weeks
2. Oral penicillin G 200 000 units twice a day
3. Oral sulfadiazine 1 gram once a day If the patient weighs less than 60 lbs the dose is 0 5 gram once a day
4. In cases of penicillin and sulfa allergies erythromycin 250 mg twice a day

For a more complete summary of AHA recommendations see reference 14

†Continuous prophylaxis is recommended for patients with a past history of rheumatic fever or for patients who have rheumatic valvular disease

of rheumatic fever and its life threatening cardiac sequellae [14] The length of time such antibiotic prophylaxis should be continued is uncertain Continued prophylaxis is indicated in certain high risk groups including military recruits, women during pregnancy and in patients with frequent exposure to children [14] Benzathine penicillin G given intramuscularly is the most effective prophylactic regimen, however, parenteral administration may be associated with a higher incidence of allergic reactions [14] The recommendations of the American Heart Association for rheumatic fever prophylaxis have been briefly summarized in Table I [14]

Prevention of bacterial endocarditis

Antibiotics are generally given prior to certain dental surgical and other manipulative procedures when these procedures are performed on areas of the body colonized by organisms likely to cause infective endocarditis The aim is to reduce the incidence or intensity of the transient bacteremia which may be associated with the procedure and to prevent colonization of damaged valves In 1923, Lewis and Grant[15] first suggested that transient bacteremia was a common event in normal individuals and that it was the presence of a deformed aortic valve that made certain individuals uniquely susceptible to endocarditis [15] Subsequent studies demonstrated that individuals with congenital, rheumatic, or other acquired valvular disease are at increased risk of developing endocarditis [16,17] Okell and Elliott[18] demonstrated bacteremia in 60 9 per cent of patients having tooth extractions The incidence of bacteremia was highest in individuals with severe pyorrhea and in those having more extensive dental work [18] Bacteremia following dental or other procedures is brief Blood cultures are generally positive for at least five minutes after the procedure and are sterile by thirty minutes There are usually fewer than 50 bacteria per ml at the peak of bacteremia [7,17,18] Studies on bacteremia following particular procedures (Table II) show considerable variation in results primarily because of the use of differing sample schedules and blood culture media Detailed reviews of this subject have recently been published [7,37] and indicate that transient bacteremia involving the indigenous bacterial flora is a common event It can be demonstrated following tooth brushing [23] while chewing candy,[38] following sigmoidoscopy,[27] and perhaps even after a bowel movement [39] The frequency and level of bacteremia may depend on local host factors For example, patients with extensive gum disease, or with infected urine at the time of a urological procedure, have a higher incidence of positive blood cultures Okell and Elliott[18] found a 10 9 per cent incidence of spontaneous bacteremia in patients with extensive pyorrhea when blood cultures were taken prior to any manipulation in patients scheduled for tooth extraction

Recommendations for antibiotic prophylaxis are based not only on the incidence of bacteremia following certain procedures but also on the ability of specific organisms to cause endocarditis Gram positive bacteria are more likely to cause endocarditis than Gram negative organisms and this may be related to their greater adherence properties Studies have shown that enterococci viridans streptococci and staphylococci adhere more readily than Gram negative bacteria to aortic valvular tissue [40] Studies are also being pursued to define specific mechanisms of adherence to host tissue [41] Antibiotic prophylaxis is therefore designed to protect the vulnerable heart valve specifically from organisms that are likely to cause endocarditis and not from the

Table II Transient bacteremia following various procedures

Procedure	Incidence of bacteremia (%)	Organisms isolated	Prophylaxis
Tooth extraction [20]	60 9-84.9	Streptococci mouth anaerobes *S epidermidis* diphtheroids	+
Dental prophylaxis	0- 8	Same	+
Tooth Brushing	0-26	Same	–
Orotracheal intubation	0	–	–
Nasotracheal intubation	16	Streptococci	–
Upper gastrointestinal endoscopy	8	Streptococci *S epidermidis* diphtheroids	–
Sigmoidoscopy[21]	9 5	Enterococci GNR†	+/–
Barium enema	11 4	As above	+/–
Liver bi psy	13 5	*S pneumoniae* GNR	–
Transurethral prostatectomy[24]	1? 3-45 7	Enterococci, GNR	+
Insertion removal of urethral catheter[25]	8 0-?6 3	Enterococci GNP	+/–
Parturition[14]	4 9	Streptococci, aerobic & anaerobic	–
Insertion, intrauterine device	0	–	–
Cardiac catheterization[26]	0	–	–
Manipulation of septic foci[27]	38 5	*S aureus* others	+

Symbols
+ prophylaxis rec mm nded
+/– prophylax recommend d by som especially f r pat ents with prosthetic heart v lves
– prophylaxis g n rally not recommended
† GNR, G am neg ti rods.

entire array of potential organisms isolated during a bacteremic episode

A number of factors limit the potential benefits of prophylaxis to only a proportion of the patients at risk Up to one third of patients presenting with endocarditis have no prior history of underlying heart disease and would not be considered for prophylaxis In one survey of individuals aware of having heart disease only 21 7 per cent appreciated the importance of communicating this information to their dentists In addition recent studies have noted that only 25 to 60 per cent of patients with endocarditis had apparent foci for their bacteremia The incidence of endocarditis due to the penicillin sensitive viridans streptococci has decreased while endocarditis caused by more antibiotic resistant organisms such as *S aureus* *S epidermidis* and enterococci has increased Finally there have been some reports of endocarditis occurring despite antibiotic prophylaxis although none of the regimens used would now be considered adequate

The actual risk of an individual with valvular heart disease developing endocarditis following a particular procedure is unknown Hook and Kaye roughly estimated the risk to be 1 in 533 (0 19 per cent) per tooth extraction Taran had four cases of endocarditis in 350 children with rheumatic valvular disease following tooth extractions while Schwartz and Salman[47] noted no cases following 403 tooth extractions in 98 patients with rheumatic heart disease The risk of endocarditis undoubtedly varies for a number of reasons including the type of valvular heart disease the age of the patient the organism involved and the level of bacteremia It should be noted for comparison that the incidence of anaphylactic reactions caused by penicillin is reported to be 0 04 to 0 11 per cent a risk similar

Table III Cardiac disorders warranting antimicrobial prophylaxis of infective endocarditis

Rheumatic valvular disease
Congenital heart disease (except uncomplicated secundum atrial septal defect)
Prosthetic heart valves
Idiopathic hypertrophic subaortic stenosis
Previous episode of infective endocarditis
Other acquired valvular heart disease (e g syphiliti arthe rosclerotic)
Patients on hemodialysis
Mitral valve prolapse
Patients with pacemakers

Need f r prophylaxis un rtain

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2 Oral penicillin G 200 000 units 3 4 times/day for ten days
3 In penicillin allergic patients erythromycin 20 mg /lb /day (up to 1 Gm /day) in divided doses for ten days

Secondary Prevention—Continuous prophylaxis†

1 Benzathine penicillin G 1.2 million units IM every four weeks
2 Oral penicillin G 200 000 units twice a day
3 Oral sulfadiazine 1 gram once a day If the patient weighs less than 60 lbs the dose is 0 5 gram once a day
4 In cases of penicillin and sulfa allergies erythromycin 250 mg twice a day

*For a more complete summary of AHA recommendations see reference 14

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of rheumatic fever and its life threatening cardiac sequellae[14] The length of time such antibiotic prophylaxis should be continued is uncertain Continued prophylaxis is indicated in certain high risk groups including military recruits, women during pregnancy and in patients with frequent exposure to children[14] Benzathine penicillin G given intramuscularly is the most effective prophylactic regimen, however, parenteral administration may be associated with a higher incidence of allergic reactions[14] The recommendations of the American Heart Association for rheumatic fever prophylaxis have been briefly summarized in Table I[14]

Prevention of bacterial endocarditis

Antibiotics are generally given prior to certain dental, surgical and other manipulative procedures when these procedures are performed on areas of the body colonized by organisms likely to cause infective endocarditis The aim is to reduce the incidence or intensity of the transient bacteremia which may be associated with the procedure, and to prevent colonization of damaged valves In 1923, Lewis and Grant[15] first suggested that transient bacteremia was a common event in normal individuals and that it was the presence of a deformed aortic valve that made certain individuals uniquely susceptible to endocarditis[15] Subsequent studies demonstrated that individuals with congenital rheumatic, or other acquired valvular disease are at increased risk of developing endocarditis[16, 17] Okell and Elliott[18] demonstrated bacteremia in 60 9 per cent of patients having tooth extractions The incidence of bacteremia was highest in individuals with severe pyorrhea and in those having more extensive dental work.[18] Bacteremia following dental or other procedures is brief Blood cultures are generally positive for at least five minutes after the procedure and are sterile by thirty minutes There are usually fewer than 50 bacteria per ml at the peak of bacteremia[7, 17, 18] Studies on bacteremia following particular procedures (Table II) show considerable variation in results, primarily because of the use of differing sample schedules and blood culture media Detailed reviews of this subject have recently been published,[7, 31] and indicate that transient bacteremia involving the indigenous bacterial flora is a common event It can be demonstrated following tooth brushing[23] while chewing candy,[39] following sigmoidoscopy,[27] and perhaps even after a bowel movement[38] The frequency and level of bacteremia may depend on local host factors For example, patients with extensive gum disease, or with infected urine at the time of a urological procedure have a higher incidence of positive blood cultures Okell and Elliott[18] found a 10 9 per cent incidence of spontaneous bacteremia in patients with extensive pyorrhea when blood cultures were taken prior to any manipulation in patients scheduled for tooth extraction

Recommendations for antibiotic prophylaxis are based not only on the incidence of bacteremia following certain procedures but also on the ability of specific organisms to cause endocarditis Gram positive bacteria are more likely to cause endocarditis than Gram negative organisms and this may be related to their greater adherence properties Studies have shown that enterococci viridans streptococci and staphylococci, adhere more readily than Gram negative bacteria to aortic valvular tissue[40] Studies are also being pursued to define specific mechanisms of adherence to host tissue[41] Antibiotic prophylaxis is therefore designed to protect the vulnerable heart valve specifically from organisms that are likely to cause endocarditis and not from the

Table II Transient bacteremia following various procedures

Procedure	*Incidence of bacteremia (%)*	*Organisms isolated*	*Prophylaxis*
Tooth extraction[5-19]	60 9 84 9	Streptococci mouth anaerobes *S epidermidis* diphtheroids	+
Dental prophylaxis [22]	0-?8	Same	+
Tooth Brushing	0 26	Same	–
Orotracheal intubation[23]	0	–	–
Nasotracheal intubation	16	Streptococci	–
Upper gastrointestinal endoscopy	8	Streptococci *S epidermidis* diphtheroids	–
Sigmoidoscopy	9 5	Enterococci GNR†	+/–
Barium enema[23]	11 4	As above	+/–
Liver biopsy[23]	13.5	*S pneumoniae* GNR	–
Transurethral prostatectomy	12 3-45 7	Enterococci GNR	+
Insertion, removal of urethral catheter[23]	8 0 26 3	Enterococci GNR	+/–
Parturition[24]	4 9	Streptococci aerobic & anaerobic	–
Insertion intrauterine device	0	–	–
Cardiac catheterization[26]	0	–	–
Manipulation of septic foci	38 5	*S aureus* others	+

Symb ls
+ prophylaxis recommended
+/– prophylaxis recommended by som especially fo patients with p osthetic he rt al es
– prophylaxis generally not recomm nded
† GNR, G am n gati e rods.

entire array of potential organisms isolated during a bacteremic episode

A number of factors limit the potential benefits of prophylaxis to only a proportion of the patients at risk Up to one third of patients presenting with endocarditis have no prior history of underlying heart disease and would not be considered for prophylaxis In one survey of individuals aware of having heart disease only 21 7 per cent appreciated the importance of communicating this information to their dentists In addition recent studies have noted that only 25 to 60 per cent of patients with endocarditis had apparent foci for their bacteremia The incidence of endocarditis due to the penicillin sensitive viridans streptococci has decreased while endocarditis caused by more antibiotic resistant organisms such as *S aureus* *S epidermidis* and enterococci has increased Finally there have been some reports of endocarditis occurring despite antibiotic prophylaxis although none of the regimens used would now be considered adequate

The actual risk of an individual with valvular heart disease developing endocarditis following a particular procedure is unknown Hook and Kaye roughly estimated the risk to be 1 in 533 (0 19 per cent) per tooth extraction Taran had

Table III Cardiac disorders warranting antimicrobial prophylaxis of infective endocarditis

Rheumatic valvular disease
Congenital heart disease (except uncomplicated secundum atrial septal defect)
Prosthetic heart valves
Idiopathic hypertrophic subaortic stenosis
Previous episode of infective endocarditis
Other acquired valvular heart disease (e g syphilitic arthe rosclerotic)
Patients on hemodialysis
Mitral valve prolopse
Patients with pacemakers

Need for prophylaxis uncertain

four cases of endocarditis in 350 children with rheumatic valvular disease following tooth extractions while Schwartz and Salman noted no cases following 403 tooth extractions in 98 patients with rheumatic heart disease The risk of endocarditis undoubtedly varies for a number of reasons including the type of valvular heart disease the age of the patient the organism involved and the level of bacteremia It should be noted for comparison that the incidence of anaphylactic reactions caused by penicillin is reported to be 0 04 to 0 11 per cent a risk similar

Table IV Antimicrobial prophylaxis of infective endocarditis

1 *Dental procedures and upper respiratory procedures*[1]
Parenteral
- A Aqueous crystalline penicillin G 1 million units plus procaine penicillin G 600 000 units IM ½ 1 hour before the procedure then penicillin V 500 mg p o q6h for 4 8 doses
- B Regimen A plus streptomycin 1 Gm IM given ½ 1 hour before the procedure[2]
- C Vancomycin 1 Gm IV over ½ 1 hour given ½ 1 hour prior to the procedure[2 3]

Oral
- D Penicillin V 2 Gm p o ½ 1 hour prior to the procedure then 500 mg p o q6h for 8 doses
- E Erythromycin 1 Gm p o 1 2 hours before the procedure then 500 mg p o q6h for 8 doses

2 *Gastrointestinal and genitourinary procedures*
Parenteral
- F Ampicillin 1 2 grams IM or IV (or aqueous crystalline penicillin G 1 2 million units IM or IV) plus streptomycin 1 0 gram IM (or gentamicin 1 5 mg /kg IM) Both antibiotics to be given ½ 1 hour before the procedure and repeated at 12 and 24 hours with the penicillin–streptomycin regimen and every 8 h for 24h with the penicillin gentamicin regimen[5]
- G Vancomycin 1 Gm IV over ½ 1 hour starting ½ 1 hour prior to the procedure plus streptomycin 1 Gm IM Both drugs may be repeated at 12 hours[5]

Oral
No oral regimen has been demonstrated to provide satisfactory protection

All dental procedures including cleaning but not including orthodontic adjustments The need for prophylaxis following tonsillectomy or bronchoscopy is uncertain
These regimens are considered the most effective and are recommended for patients with prosthetic heart valves and for individuals on long term penicillin prophylaxis for rheumatic fever
These regimens may be used in penicillin allergic patients. The parenteral regimen is preferred
Prophylaxis is recommended for all genitourinary procedures including urethral catheter insertion and removal It is also recommended for gall bladder and bowel surgery It is not routinely recommended for sigmoidoscopy barium enema liver biopsy or upper g.i. endoscopy except perhaps for patients with prosthetic heart valves
Dosage of streptomycin and gentamicin should be modified in the presence of renal insufficiency

to that of endocarditis following tooth extraction[48 49]

The recommendations for antibiotic prophylaxis for endocarditis have been extensively revised based on experimental studies using a rabbit endocarditis model Endocarditis is produced in the rabbit by passing a polyethylene catheter across the aortic or tricuspid valves and giving an intravenous injection of organisms after a period of 1 to 2 days[50 51] Mechanical trauma to the valve leads to formation of a platelet-fibrin thrombus which serves as the nidus for infection The virulence of the organism correlates with the likelihood of establishing an infection following the 'transient' bacteremia Durack and Petersdorf[9] have studied the more commonly recommended regimens for prophylaxis using this model Antibiotics were given one half hour prior to the injection of organisms Rabbits were killed at 24 hours at which time bacterial colony counts of valvular vegetations were performed Their studies of streptococcus viridans endocarditis demonstrated that vancomycin alone, or a combination of penicillin G and streptomycin were the most effective regimens When a lower initial bacterial inoculum was used, erythromycin was shown to have some protective value, however primarily bacteriostatic drugs such as tetracycline clindamycin, or erythromycin were generally ineffective[8 9] Similar studies were performed in rabbits inoculated with enterococci[10] Vancomycin alone and vancomycin or ampicillin plus streptomycin were all effective regimens There was considerable variation in response depending on the strain of enterococcus these variations were not always predicted by in vitro sensitivity tests[10] The studies in the rabbit model provide important data for selecting an appropriate prophylactic regimen but with some appreciable limitations The pharmacokinetics of antibiotics in the rabbit are different from those in man Endocarditis is produced in the rabbit by leaving a foreign body, the catheter across the cardiac valve Finally a high inoculum of bacteria 10[8] colony forming units/ml is used compared to the 10[1] to 10 colony forming units/ml generally encountered in the bacteremia following dental procedures[7 23] The high inoculum assures that a higher percentage of animals will be infected however it provides a greater challenge for the prophylactic regimen, making some drugs such as erythromycin which are effective at a lower inoculum, appear inadequate Therefore regimens shown to be effective using this experimental model probably provide a wide margin of safety Nevertheless some have suggested that antibiotic dosages for prophylaxis should be the same as those used for treatment of endocarditis[17]

Present recommendations for the prevention of bacterial endocarditis

Despite some uncertainty about effectiveness antibiotic prophylaxis for bacterial endocarditis is recommended in association with certain procedures The morbidity and mortality of the disease *outweighs concern for drug side* effects and for the limited protection they may provide Prophylactic regimens suggested for dental or oropharyngeal surgery are aimed especially against viridans streptococci while those suggested for genito-urinary or gastrointestinal procedures are directed primarily against the enterococcus[33, 2]

There are several precautions that should be taken in individuals with underlying valvular disease Patients should be informed of the potential risks of dental gastrointestinal or genitourinary procedures Cardiac conditions which warrant prophylaxis are listed in Table III Good dental care is particularly important in patients with valvular heart disease The level of bacteremia is correlated with the extent of gum disease Oral irrigation devices should generally be avoided in patients at high risk for endocarditis because of the increased incidence of bacteremia associated with their use[2] Patients scheduled for elective valvular replacement should have any necessary dental work performed prior to cardiac surgery since the risk of developing endocarditis in the immediate postoperative period is 2 to 4 per cent[7] When procedures are performed on the genito-urinary or biliary systems the incidence of bacteremia is reduced when the urine or bile are sterile[39] If tracheal intubation is required the orotracheal approach causes less bacteremia than the nasotracheal approach[2]

The antibiotic regimens listed in Table IV are based on the recently published recommendations of the American Heart Association[5] and *The Medical Letter on Drugs and Therapeutics*[3] Antibiotics given parenterally are probably more *effective than those given by mouth*. The recommendations represent an attempt to accommodate the practical problem created by giving parenteral therapy for outpatient procedures with the need for sustained antibiotic activity *The parenteral regimen using* intramuscular penicillin G plus procaine penicillin is probably adequate for most cardiac patients undergoing dental procedures However patients taking oral penicillin prophylaxis for rheumatic fever have a higher incidence of relatively penicillin resistant streptococci in their oropharynx so that coverage with vancomycin or penicillin plus streptomycin is advised In addition the latter regimens are *recommended for patients with prosthetic valves* Antibiotic coverage is recommended for surgery on abscesses or infected foci and for debridement of burned tissue The antibiotic regimen in such instances should take account of the organisms (i e *S aureus*) likely to be associated with bacteremia and endocarditis[52]

Prophylaxis in cardiac surgery

Antibiotic prophylaxis is often recommended in cardiac surgery even though large carefully controlled studies of the effectiveness of such *regimens are not available* Antibiotic coverage has been suggested because of the high mortality associated with early prosthetic valve endocarditis[5, 5] The incidence of valvular infections is relatively low[4] so that a large number of patients would have to be included in any study evaluating the potential benefit of prophylactic antibiotics

The incidence of prosthetic valve endocarditis rises in patients requiring prolonged surgery and cardiopulmonary bypass[56] Although the organisms accounting for these infections vary in different institutions the most frequently isolated pathogens are *S epidermidis S aureus* diptheroids fungi (especially Aspergillus and Candida sp) and Gram negative rods[4, 55] The patient s skin the operating room air and the cardiopulmonary bypass machines have been identified as possible *intraoperative sources of* infection while intravenous and urinary catheters remain the major postoperative portals of entry for bacteremia[4, 55, 5]

Two recently reported studies have compared regimens using antibiotic prophylaxis continued for 1 to 2 days versus 5 to 6 days following *cardiac* surgery and found no significant differences in the incidence of serious infection between the two *groups*[57, 58] *One study* noted more infections caused by resistant organisms with the longer regimen[57] The increase *in early prosthetic* valve infections caused by Gram negative organisms and methicillin resistant *S epidermidis* noted *recently* may be a consequence of the selective pressure provided by prophylactic therapy[5]

Antibiotic coverage is unnecessary for pace

maker insertions, closed heart surgery, and cardiac catheterization [36, 56, 60] It is suggested for open heart surgery when cardiopulmonary bypass is necessary Although a penicillinase resistant semisynthetic penicillin or a cephalosporin given parenterally for 48 hours is recommended, differing local patterns of antibiotic sensitivity may warrant additional or different antibiotic coverage [52]

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Annotations

Conflicts in coronary care

There appears to be no agreement as to what constitutes proper care of a patient with acute myocardial infarction Styles of coronary care vary from the hands off peace and quiet approach advocated by Burch and associates[1,2] to the active measure all approach of Forrester and colleagues[3] and others in specialized research units Some claim that specialized coronary care in hospital confers no advantage over management in a general hospital ward[4] Some suggest that many patients can best be managed at home from an early stage The matter is confused by quoted mortality rates for the acute event which range from under 10 per cent to over 40 per cent—and the fact that some of the lowest quoted rates are from patients treated at home or in general medical wards and some of the highest rates are from specialized coronary care wards[6] Indeed two oft quoted articles describing advances in coronary care showed mortality rates of 26 per cent[7] and 34 per cent The sceptic is entitled to ask if these are really advances at all—or alternatively are some advantages cancelled by disadvantages and hazards of other therapeutic or monitoring procedures?

Despite the queries the consensus appears to be that coronary care in principle is a good thing and merits widespread implementation Most observers would explain the differences in quoted results as being due to differences in selection of patients or in classification of myocardial infarction The biggest question appears to be—what type of coronary care can give greatest benefit at reasonable cost?

The coronary care we have been able to provide at this hospital appears to achieve a happy compromise between comfort efficacy and cost The coronary care ward has 30 beds and is divided into an acute six bed area and a 24 bed subacute area Electrocardiographic monitoring is provided for all beds in the acute area and 12 beds in the subacute area Patients are admitted to the acute section of the ward and proceed thence in the same bed to the subacute section whence they are discharged home usually after 10 to 21 days In the acute section patients have the privacy of a single room furnished with carpet drapes and a mural to resemble as much as possible a home or hotel room After transfer patients are monitored with ECG for several days usually in a six bed ward where they see others disconnected from the ECG and view this when their turn comes as a sign of progress This arrangement appears to provide the proper measure of comfort and confidence at the right time and gauged by the rough and ready measure of gift boxes of chocolate per week has achieved better acceptance than management in any other part of the hospital

Total nursing complement of the ward is 35 nurses (18 trained and 17 trainee) nursing staff rotate through the whole ward and have the professional and personal satisfaction of being able to follow patients to discharge There are two medical officers and one technician in the acute section of the ward Staffing of the whole ward is only somewhat higher than other wards of the hospital while average bed occupancy at 85 per cent is only marginally lower In this ward and without altering staff arrangements we have been able to introduce various advances including hemodynamic monitoring (some 300 patients so managed over 5 years) and arterial counterpulsation[10] (112 patients treated over 5 years) Mortality rate for all patients with infarction admitted direct over a recent 2 year period was 9 8 per cent while for all such patients under 65 mortality rate was 5 7 per cent[9]

Our experience leads us to believe quite firmly that specialized coronary care is most desirable and that it is possible to provide this at a high level with good results at reasonable cost and with high patient comfort Above all we believe that comfort cost and efficacy need not be in conflict

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Of the venous pumps and congestive heart failure

Patients with left ventricular congestive heart failure (CHF) develop dyspnea upon walking and running This is attributed to failure of the left ventricle to pump blood forward out of the lungs. But could it not also be due in large part to the venous pumps in the legs which return the blood to the right side of the heart and into the lungs where it accumulates more rapidly than the left ventricle can remove it? There are no valves in the circulatory system to prevent the blood from flowing centrally into the lungs This "congestion" of the lungs due to the venous pumps in the extremities could contribute greatly to the production of the dyspnea caused by exercise When such a patient is sitting or lying quietly and the venous pumps in the legs are inactive he is much less congested with blood in the lungs and he is much less dyspneic Therefore what about the venous pumps exercise and the symptoms and signs of CHF?

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Renal vein renin and saralasin testing in renovascular hypertension

In the management of renovascular hypertension a major problem lies in deciding which patients are potentially curable by surgery Various tests have been devised to identify such patients These tests have included peripheral renin determinations renal vein renin estimations and more recently the use of angiotensin II antagonists

Peripheral renin activity does not reliably predict the response to renovascular surgery as there have been many reports of patients with normal or low values who have had good results from such surgery

The use of renal vein renin measurements in hypertensive patients with unilateral renal artery stenosis has an accuracy of about 85 per cent in predicting the effect of surgery on hypertension However false negative results are a major problem and various stimuli of renin release have been employed to bring out significant differences between the involved and contralateral kidneys These stimuli have included dietary sodium restriction maintenance of the erect posture during testing and such drugs as furosemide nitroprusside hydralazine and diazoxide

Our group favors the use of diazoxide stimulation of renal vein renin levels We now have adequate follow up information on 12 patients with *unilateral* renal artery stenosis who were submitted for renovascular surgery following determination of their renal vein renin ratios Six of the 12 had significant renal vein renin ratios (ratio of involved to contralateral side ≥ 1.5 1) before diazoxide which were accentuated following diazoxide administration Of these six patients five have had anatomically successful renovascular surgery The blood pressure response to surgery was classified as improved in four and failed in the fifth, a patient who had evidence of bilateral renal parenchymal disease In the remaining six operated patients, the renal vein renin ratio only became significant following diazoxide administration the ratio changing from a mean of 1.1 1 before to 3.3 1 after diazoxide In five of these cases, renovascular surgery was anatomically successful Hypertension was *cured* in four and improved in one Thus diazoxide stimulation is more reliable than the unstimulated renal vein renin ratio in predicting a successful response to renovascular surgery Moreover this procedure has proved safe in our experience of approximately 100 cases including 42 with renal artery stenosis (unilateral or bilateral)

The angiotensin II antagonist saralasin has been widely used in an effort to identify potential responders to renovascular surgery Lack of a depressor response to saralasin is said to reliably exclude angiotensin mediated hypertension and it has been stated that surgery should not be undertaken in non responders However renovascular surgery has been reported to produce successful results despite negative saralasin tests in two patients in which significant renal vein renin ratios were found From this and our own experience we believe that false negative saralasin responses do occur In three hypertensive patients with unilateral renal artery stenosis we failed to demonstrate a blood pressure fall following saralasin The saralasin tests were performed using the protocol of Streeten and associates and each patient was significantly sodium depleted prior to testing The patients *all* had non lateralizing renal vein renin ratios initially but following diazoxide the ratio became significant in every case All three have had excellent blood pressure responses to renovascular surgery Thus diazoxide stimulated renal vein renin ratios appear superior to saralasin testing in predicting the blood pressure response to renovascular surgery

Reliance on saralasin testing as a means of excluding renin angiotensin system overactivity has caused some problems. Results of renovascular surgery have recently been reported in two patients with renal artery stenosis who had negative saralasin tests non lateralizing renal vein renin ratios and low peripheral renin values Both had a satisfactory blood pressure response to surgery Because of failure to demonstrate overactivity of the renin–angiotensin system in these patients it was claimed that they had a new syndrome of non renin mediated renovascular hypertension However such overactivity was not convincingly excluded in these two patients First as above false negative saralasin tests are

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possible and second the renal vein renin tests were performed in the supine position and after administration of oral furosemide (1 mg/Kg body weight) on the afternoon before the test Such slight stimulation of the renal vein renin ratios may have been inadequate to demonstrate overproduction of renin by the involved kidney Thus although there is some evidence to support the existence of such a syndrome in various animal models[11] its existence in man still remains to be conclusively proven

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Towards more selective resuscitation

The reviving of the apparently dead has long been a popular subject in the public imagination particularly since the development of closed chest massage and external defibrillation Physicians must be prepared to analyze the results in order to avoid being carried away by the excessive enthusiasm generated by even an occasional success It is essential for due regard to be given to the most efficient employment of resources and to the suffering inflicted on the relatives of patients when prolonged attempts at resuscitation are made in the face of an inevitably hopeless outcome

Resuscitation is more likely to be successful in coronary and intensive care units and there is no doubt that in such circumstances a very energetic policy must be pursued In the more general areas of the hospital however the position is less clear A ten year survey of the results of resuscitation in such areas has recently been carried out at the Central Middlesex Hospital in London[1] The cases studied were those treated by the hospital s cardiac arrest service excluding patients in the coronary care and intensive therapy units Successful resuscitation was defined as survival of the patient to be discharged alive from hospital In the ten year period there were 93 survivors out of 1 063 cardiac arrest cases The 80 patients from the first nine years of the survey were followed up for at least one year and information was collected about their subsequent health An actuarial life table showed an annual mortality rate of 7 per cent in the survivors a figure similar to that following uncomplicated myocardial infarction Assessment was made of their physical condition and only four of the 80 subjects showed significant deterioration of their health or working capacity due to the arrest and all these four died within 30 months of it In the remaining survivors the good quality of life was impressive

The most significant factor influencing the outcome is the primary diagnosis The success rate ranges from 22 per cent in drug overdose cases to 20 per cent in surgical cases and 15 per cent in myocardial infarction cases. In contrast following severe generalized trauma or advanced neurological disease the success rate was less than 2 per cent Patients whose arrest complicated such conditions as cardiac failure pulmonary embolism or respiratory failure fell into an intermediate group of between 4 per cent and 8 per cent There were no long term survivors after cardiac arrest as a complication of head injury or subarachnoid hemorrhage

Thirty six per cent of the arrests occurred in the Accident and Emergency Department 58 per cent were in the wards of the hospital and most of the remainder in the operating theatres The over all success rate was highest in the Emergency Department but this was due entirely to the large number of cases of myocardial infarction who suffered cardiac arrest there Of the 93 survivors of the whole series 54 had arrested due to myocardial infarction in the Emergency department

The majority of the patients included in this series were aged between 50 and 70 years Because of the concentration of the more favorable diagnostic categories in this age group the success rate was highest in these two decades In earlier decades respiratory traumatic and neurological causes were predominant with fewer survivors[1] The numbers of cases of myocardial infarction in the Emergency Department were sufficiently large to show that age was without influence on

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the survival rate in that particular category Attempts at resuscitation were made in 216 patients over the age of 70 with a long term survival rate of 4 7 per cent

Although the over all success rate in this large series was low the subsequent general condition and life expectancy of the survivors was good The findings suggest that greater emphasis must be placed on the circumstances of each arrest Clearly the primary diagnosis is paramount and rather less attention should be paid to location or in particular to the age of the patient The best service must be provided in the Emergency Department and a policy of energetic resuscitation should be mandatory there In other parts of the hospital, and especially in certain diagnostic categories the results of resuscitation are so poor that a much more selective approach would appear to be indicated

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possible and second the renal vein renin tests were performed in the supine position and after administration of oral furosemide (1 mg /Kg body weight) on the afternoon before the test Such slight stimulation of the renal vein renin ratios may have been inadequate to demonstrate overproduction of renin by the involved kidney Thus although there is some evidence to support the existence of such a syndrome in various animal models [1] its existence in man still remains to be conclusively proven

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Table I Hemodynamic findings (mean ± SD and range) before and after hyaluronidase intravenous bolus

	−30 min	−15 min	0	15 min	30 min	60 min
HR bt./min	88 6 ± 11 4	86 5 ± 9 3	87.3 ± 11 9	87 3 ± 10 4	88 4 ± 10 1	88 0 ± 13 6
	(66-105)	(67 105)	(67 108)	(68 102)	(66 104)	(62 112)
BP mm. Hg	106 5 ± 18 9	104 8 ± 14 7	106 2 ± 22 5	101 0 ± 16 7	103 0 ± 18 0	104 7 ± 14 3
	(75 134)	(76 130)	(74 136)	(73 124)	(72 129)	(85-128)
$\overline{RAP}$ mm. Hg	7 2 ± 5 9	7 5 ± 6 3	7 6 ± 6 1	7 7 ± 6 1	8 0 ± 6 4	8 6 ± 6 7
	(2 19)	(2 19)	(2 19)	(2 19)	(2 20)	(2 19)
PAedP mm. Hg	18 1 ± 3 2	19 2 ± 3 5	18 4 ± 3 1	18 7 ± 2 9	19 1 ± 3 3	18 7 ± 2.5
	(13 2?)	(12 2)	(12 22)	(13-2?)	(14 23)	(15 ?2)
CI L./min /M	2 6 ± 0 4	2 7 ± 0 6	2 7 ± 0 5	2 8 ± 0 5	2 6 ± 0 4	2 6 ± 0 5
	(2 1 3 5)	(2 0-3 6)	(2 0 3 4)	(2 2 3 4)	(2 2 3 7)	(2 1 3 5)

cated some aspects of the drug s mechanism of action on the damaged area

To acquire further information in this regard and to evaluate eventual undesirable hemodynamic effects we recorded hemodynamic data in eight patients after hyaluronidase administration in the course of a multicenter study on the effects of the drug on the electrocardiographic signs of necrosis in patients with acute myocardial infarction Pulmonary arterial pressure (PAP) systemic pressure (BP) and right atrial pressure (RAP) were recorded continuously using an XM 5101 Philips apparatus with Statham P23 transducers for 30 minutes preceding the administration of the drug and for 60 minutes afterwards Cardiac output was assessed by thermodilution method at −30 minutes −15 minutes 0 +15 minutes, +30 minutes and +60 minutes with respect to administration The hyaluronidase 500 U /Kg was injected as an intravenous bolus within 8 hours from symptom onset In five patients the catheters were left in place and the hemodynamic evaluation was repeated 6 hours later after a second dose administered in an identical fashion Therefore the hemodynamic effects of hyaluronidase were observed after a total of 13 doses Six patients had a pulmonary artery end-diastolic pressure (PAedP) >18 mm Hg a value that we consider critical in identifying patients with definite left ventricular dysfunction Three patients had a $\overline{RAP}$ >10 mm Hg and three a cardiac index (CI) <2 5 L /min /M Two patients showed clinical signs of heart failure

The data obtained are presented in Table I Only minimal changes, none of statistical significance were observed in the hemodynamic parameters Thus it can be concluded that the action of hyaluronidase in limiting the development of necrosis is not attributable to hemodynamic modifications involving the cardiovascular system in its entirety The innocuousness of the drug from a hemodynamic point of view demonstrated also in patients with heart failure is important since it renders possible administration to the patients with acute myocardial infarction regardless of their hemodynamic status.

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Testing antianginal therapy In favor of current practice

To the Editor

Requirements for testing efficacy of antianginal treatment include documentation of disease in patients with frequent episodes of anginal pain (severe stable disease) pain nitro

Letters to the Editor

Neurologic–cardiologic interrelationships

To the Editor

Considering the many recent articles pointing out the connections between the neurologic and cardiovascular systems, it seems as though we might need to start a new specialty of cardio neurology or neuro cardiology I am sure there would be a fight for top billing

This interrelationship might be the basis for many at present puzzling phenomena For example it has seemed quite possible to me that the sudden infant death syndrome could be a cardiac arrhythmic or apneic event secondary to a minor seizure disorder s discharging through the autonomic nervous system

In support of this I have only personally investigated two cases of sudden infant death syndrome and there was a positive family history of seizures in both cases in the mother in one and in the sister in the other

Certainly even two swallows do not make a summer It does seem worth investigation however

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Nitroprusside reversal of ergotamine induced ischemia

To the Editor

We would like to report briefly a severe adverse reaction to ergotamine and an equally dramatic reversal with nitroprusside administration

A 55 year old woman was being treated by her family physician for migraine headaches anxiety and a possible gastric ulcer She was prescribed Cafergot suppositories (ergotamine 2 mg and caffeine 100 mg) over a period of 7 days prior to this admission She received one suppository daily

She was referred for further evaluation because of a rather sudden onset of pain in both feet which had persisted during the past 48 hours prior to admission The major physical findings revealed (1) the legs were warm (2) the ankles and feet were cool dry and cyanotic and (3) the posterior tibial pulses were faint and the dorsalis pedis pulses were absent Due to the absent pulses and striking ischemia a percutaneous aortogram was performed and revealed smooth but small arteries distal to the bifurcation of the aorta There was narrowing of the superficial femoral artery as it entered Hunter s canal For the patient s size the arteries were definitely considered diminutive

The diagnosis of ergotism was made and treatment was initiated with an intravenous infusion of low molecular weight dextran 15 c c /minute heparin 5 000 units intravenously every 4 hours and ganglionic blockade by an extra dural anasthetic Despite these measures her legs continued to be quite painful and cyanotic and the skin became purple in appearance over the toes and on the bottom of her feet in a fashion characteristic of severe ischemia

After approximately 12 hours and a fear of gangrenous changes in both feet it was decided to try an intrarterial infusion of sodium nitroprusside (Nipride) The solution was prepared by adding 50 mg of nitroprusside in 250 c c D₅W and it was infused in each femoral artery through an intra arterial catheter at a rate of 30 drops/minute Over a period of approximately 10 minutes there was a dramatic and incredible improvement in the color of her feet and both dorsalis pedis pulses became palpable The infusion was gradually discontinued over the next 12 hours with relief of pain and continued findings of adequate perfusion

The syndrome of vascular insufficiency secondary to ergotamine has been known to produce gangrene requiring amputation[1] and in the current ca e it was being considered as a distinct possibility Intravenous nitroprusside has been previously reported to reverse ergotamine induced ischemia of all four extremities[2] Our rationale for infusing nitroprusside intrarterially was based on a presumption that smaller doses would be required and hypotension avoided It is possible that an intravenous infusion would have been equally as safe and efficacious however it could not have been more gratifying

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Evaluation of the hemodynamic effects of hyaluronidase in patients with acute myocardial infarction

To the Editor

The beneficial effect of hyaluronidase in reducing the electrocardiographic signs of ischemic damage in the initial phase of acute myocardial infarction and in limiting the subsequent development of necrosis have recently been shown both in experimental animals[1] and in man with acute myocardial infarction[3] Experimental studies[1] have indi

Table I Hemodynamic findings (mean ±SD and range) before and after hyaluronidase intravenous bolus

	−30 min.	*−15 min*	*0*	*15 min.*	*30 min*	*60 min.*
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BP mm. Hg	106 5 ± 18 9 (?5 134)	104 8 ± 14 7 (76 130)	106 2 ± 2?.5 (74 136)	101 0 ± 16 7 (73 124)	103 0 ± 18 0 (72 1?9)	104 7 ± 14 3 (85-128)
$\overline{RAP}$ mm. Hg	7.2 ± 5 9 (2 19)	7 5 ± 6 3 (? 19)	7 6 ± 6 1 (2 19)	7 7 ± 6 1 (2 19)	8 0 ± 6 4 (? 20)	8 6 ± 6 7 (2 19)
PAedP mm Hg	18 1 ± 3 ? (13 2?)	19 2 ± 3 5 (1? 22)	18 4 ± 3 1 (12 2?)	18 7 ± 2 9 (13-22)	19 1 ± 3 3 (14 23)	18 ? ± 2 5 (15 ??)
CI L./min /M	2 6 ± 0 4 (? 1 3 5)	2 7 ± 0 5 (2 0 3 6)	2 7 ± 0 5 (2 0-3 4)	2 8 ± 0 5 (2 2 3 4)	2 6 ± 0 4 (2.2 3 7)	2 6 ± 0 5 (? 1 3 5)

cated some aspects of the drug s mechanism of action on the dama ed area

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Testing antianginal therapy In favor of current practice

To the Editor

Requirements for testing efficacy of antianginal treatment include documentation of disease in patients with frequent episodes of anginal pain (severe stable disease) pain nitro

glycerin diaries randomization procedures and exercise stress tests Traditionally the history of symptoms was held adequate for evaluation of the impact of a new therapy The complexities in analyzing life stresses emotions activity levels and the like have led to the suggestion that subdividing the history and rating each aspect might provide even more meaningful data before and during active therapy Another opinion of one fed up with the subjective variability inherent in angina pectoris is that full reliance in therapeutic evaluations be placed on standardized stress test results

It seems clear that both subjective and physiological status of the patient with ischemic heart disease must be measured They probably provide different types of information which summate into each patient s anginal syndrome The patient who reports pain during sexual activity but who can exercise safely to a heart rate of 160/minute in the laboratory—is he a formidable sexual athlete or is he telling his physician only of his desires?

We have recently had an opportunity to measure the subjective and objective results of randomization to treatment in reliable patients with severe angina pectoris this is critical in evaluating the effects of any form of therapy [2] After randomization to placebo therapy in both 2 week and 4 month trials patients reported mean decreases in pain frequency and nitroglycerin consumption which barely distinguished them from comparable patients randomized to active drugs During the pre randomization baseline observation period of one study seven of 17 patients abruptly withdrawn from propranolol reported gross increases in pain frequency and nitroglycerin consumption In all three instances of significant alteration in subjective data results of standardized maximal stress tests were nearly stable In contrast those patients randomized to active drug treatment demonstrated statistically significant improvement in their performance during exercise tests as well as slightly less pain than placebo patients

It appears as if the combination of technics of observation allows dissection of two important but inconsistently related aspects of coronary arterial obstructive disease Can we do without one or the other? I think not

The diary of pain and nitroglycerin consumption whether complex or simple relates something of the subjective as well as functional status In addition diaries can provide critical information about adverse drug reactions or change in disease status i e onset of unstable angina before the patient or the physician may discern these alterations in the exercise laboratory

The objective testing of functional capacity and the exercise electrocardiogram provide critical measurements which have generally been accepted as necessary to the description of the effects of therapy on resting submaximal and maximal cardiovascular physiology

Thus it appears as if there is no short cut to the trying problem of testing effective antianginal treatment It continues to be essential to record both subjective and objective data obtained from reliable patients undergoing suitable test protocols With both types of information being collected however trials on patients with milder disease may be worth carrying out Those with fewer attacks (e g 1/wk vs 5 to 10/wk) may have coronary arteries and cardiac muscles which may be more profoundly affected by certain drugs particularly vasodilators Such trials may have to be longer than a few weeks and the training effect must be avoided but the data may be more valuable than that obtained from patients with calcified thread like vessels and extensively damaged muscles

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Prolonged repolarization and hypomagnesemia

To The Editor

We read with interest the exhaustive review by Burch and Giles of hypomagnesemia in cardiovascular diseases (AM HEART J 94 649 1977) They have stressed the occurrence of flat T waves and prominent U waves A review of case reports of patients all of whom had hypomagnesemia revealed that prolonged QT interval was seen in all these cases [1-3] All of them responded to magnesium therapy The prolonged QT interval appears to be a T + U complex where T is flat and U is prominent This prolonged repolarization in these cases also seems to be associated with increased irritability of myocardium giving rise to ectopic activity bigeminal rhythm and ventricular fibrillation Another interesting phenomenon of electrical alternation of T wave and U wave had also been noted

Therefore we feel that the occurrence of these changes should be watched for and treated promptly especially in chronic alcoholic patients as these changes are definite antecedents of ventricular fibrillation

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CPK MB elevations in hypothermia

To the Editor

I was rather puzzled to read the report of Carlson and associates in the March issue of the AMERICAN HEART JOURNAL (95 35 1978) Creatine phosphokinase MB isoenzyme in hypothermia Case reports and experimental studies

In the past 50 patients subjected to cardiopulmonary bypass and hypothermic cardiac arrest myocardial temperatures have been maintained less than 20 C for periods of up to 170 minutes All patients had CPK MB estimations performed immediately postoperatively together with LDH isoenzymes Only one patient had CPK MB elevation greater than two per cent This patient had no evidence of myocardial infarction by other criteria

Our experience and the experience of many other cardiac surgeons using hypothermic cardioplegic cardiac arrest techniques is at variance with that of Carlson and associates It appears unlikely that hypothermia itself was responsible for the CPK MB elevations in their patients

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Reply

To the Editor

We thank Dr Maggs for his comments on our article Creatine phosphokinase MB isoenzyme in hypothermia (AM HEART J 95 35 1978) In reply we would like to make the following observations

In our paper we presented six patients with hypothermia and MB CPK in their serum without clinical evidence of myocardial infarction We presented experimental evidence that six hours of total body hypothermia were sufficient to result in a 21 per cent loss of myocardial and striated muscle CPK activity in the dog There are fundamental differences between our observation and those Dr Maggs has presented

Our patients and the experimental animals were subjected to prolonged hypothermia much longer than the 170 minutes experienced by Dr Maggs patients Certainly the duration of exposure relates to the extent of any injury

Second the two mechanisms of hypothermia environmental in our cases versus bypass induced have different patterns of cooling

Finally the biggest difference is that the hearts of our patients continued to perform work during hypothermia and continued to be perfused Muscle death and consequent enzyme release occurs more readily under conditions of a higher oxygen consumption In addition Hansson observed differing lymphatic enzyme release patterns depending on the conditions of coronary perfusion and the circumstances of hypothermic arrest

From Dr Maggs letter we feel the only conclusion to be drawn is that under certain conditions of hypothermic cardiac arrest restoration of cardiac function can be made without MB-CPK appearing in serum and presumably without myocardial damage This seems even more remarkable when the duration (2 hours) and extent (20 C) of hypothermia is considered Under other less controlled conditions such as we observed hypothermia with continuing cardiac activity may result in diffuse myocardial damage.

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Recourse to a computer for teaching the proper use of nitroglycerin

To the Editor

The physician now possesses an expanded therapeutic armamentarium for combating angina pectoris including long acting vasodilators beta adrenergic blocking drugs exercise conditioning and the coronary bypass operation But we believe the proper use of sublingual nitroglycerin continues to be the mainstay of correct therapy This looms with even greater importance now for when chest discomfort is deemed inadequately controlled, the patient is invariably directed to a costly operative procedure Indeed the correct use of nitroglycerin may very well have obviated more drastic interventions

The problem relates in part to the fact that nitroglycerin unlike many other medications is not taken on a fixed schedule The decision for its use is up to the patient Folk wisdom dictates that drugs be used sparingly lest loss of efficacy or habituation supervene There is also a psychologic need to deny that retrosternal or epigastric discomfort is related to the heart The patient is generally aware that the prompt relief afforded by nitroglycerin confirms the cardiac source for the discomfort Furthermore the occasional need to use nitroglycerin in public calls attention to the personal disability when among colleagues this may raise disquiet as to one continuing capacity to perform when among family members, it may provoke anxiety and encourage unwarranted solicitude These and similar factors militate against the free use of nitroglycerin In fact it is a constant source of consternation that only half of our patients with angina resort to nitroglycerin appropriately

To improve patient performance we have devised an interactive computer teaching program The patient is seated in front of a television screen and instruction is given in the use of a few keys on a connecting typewriter key board The program begins by asking several multiple choice or true false questions on the frequency of angina the customary use of nitrates and the specific indications for their use Responses are indicated by typing numbers on the keyboard The computer then presents information about nitroglycerin in a succession of brief written messages appearing on the televi

This w k was supported in part by G ant No HS 00188 from th Nat nal Cente fo H alth Services Research Un ted St tes Public Health Serv e

sion screen At intervals the patient is confronted with questions based on the material already presented The patient is complimented for correct answers If the response is improper additional explanations are provided and the relevant material is reviewed The interview is written so as to endow the machine with a friendly personality The aim is to convey an optimistic outlook and to foster insight into factors which contribute to angina Those who learn quickly complete the program in about 30 minutes Others may repeatedly review certain points and require an hour or more A pamphlet is given to the patient for review at home

Fifty consecutive patients with angina who viewed the computer program were sent a brief questionnaire by mail three months later to determine whether a single exposure modified nitroglycerin use Forty four of 47 patients who continued to experience angina responded During this interval the frequency of angina was not modified thus 21 who had at least one or more episodes daily before the program experienced the identical number after the program The following table presents the essentials

Table I

	Computer program (No of patients)	
	Before	After
Taking nitroglycerin	34	41
For severe or prolonged pain only	16	9
For mild discomfort at the very onset or in anticipation	18	32

A change occurred in the basis for nitroglycerin consumption fewer patients waited for severe pain and more took the drug in anticipation However these numbers do not fully convey the altered attitude fostered by the computer program Perhaps more instructive are the following verbatim responses that communicate the new attitude

(a) Since I viewed the computer program I have been taking nitroglycerin for no reason just to prevent my angina and I have found since doing this I have had no pain or discomfort and I even feel better I think the secret of feeling good and without chest discomfort is to take nitroglycerin when not needed

(b) I learned to stop counting how many I take daily—counting made me try to do without and wait for pain to pass

(c) The nitroglycerin program has made me aware of stress situations creating in many instances an angina problem and I am now able to control the angina with the nitroglycerin where before I used it only in severe discomfort and usually ended up with a hospital visit It is now not a last resort medication

This experience indicates that an interactive computer teaching program can effectively supplement physician instructions on the proper use of drugs Even patients who had been carefully and repeatedly counseled in the use of nitroglycerin were less inhibited as a result of exposure to the computer teaching program There are a number of advantages to the computer it is not impatient does not lack time consistently presents all the material and can review numerous times with the tempo determined exclusively by the patient s speed of comprehension An important additional reason for the computer s success is that the patient is not passive is not merely exposed to a soliloquy but engages in a dialogue with the physician s surrogate In short this is a method inexpensive in both cost and time to foster a new attitude towards a most beneficial medication

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Potential hazard of the programmable pacemaker

To the Editor

The Omni Stanicor programmable pacemaker has features that are highly desirable to the physician The rate and current output of this pacemaker can be changed at any time by a non invasive technique involving electromagnetic pulse trains emitted by an external programmer This adjustment in the rate and power output can be made as the patient s requirements change By decreasing the current output the pacemaker s longevity is increased The adjustable rate control facilitates control of complicating arrhythmias

Prolongation of battery life is a laudable feature of the programmable pacemaker However it is also important to remember to increase the milliamperage when a myocardial infarction occurs

A programmable pacemaker was implanted in an 80 year old woman on February 10 1976 because of severe sinus bradycardia with sinus arrests The pacemaker was reprogrammed to 4 MA with a rate of 70 on December 23 1976 Periodic telephone transmissions of the electrocardiogram revealed perfect function of the pacemaker During the months of September October and November 1977 weekly transmissions were accomplished and no pacing or sensing malfunctions were noted On December 7 1977 she developed severe chest pain which led to her admission to the Coronary Care Unit at The Methodist Hospital An electrocardiogram revealed perfect pacemaker function Occasional unpaced beats however showed a new right bundle branch block with deep T wave inversions in Leads V to V A subendocardial infarction appeared likely and this was substantiated by the increase in the CPK SGOT and LDH On the second hospital day pacemaker spikes were observed on a monitor lead which were not followed by QRS complexes The patient then developed ventricular tachycardia and ventricular fibrillation and was successfully cardioverted (Fig 1) After the restora

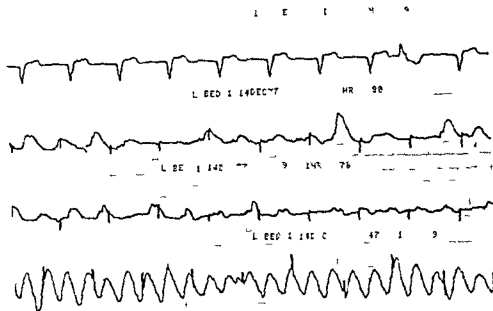


Fig 1 *Upper ECG panel* shows perfect pacemaker function *The next two panels* show the pacemaker artifact which is not followed by paced beats *The bottom panel* shows the onset of ventricular tachycardia

tion to sinus rhythm the patient remained in coma due to severe brain damage The pacemaker was re programmed to 9 MA and over the next seven days the pacemaker continued to work properly The patient finally succumbed to a complicat ing pneumonia

This case is important because it reminds us to in rease the milliamperage when a patient sustains a myocardial infarc tion With this complication the pacing threshold increases Similarly the pacing threshold may have to be increased in the presence of severe electrolyte abnormalities

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Heart rate correction of pre ejection period

To The Editor

The paper by Burckhardt and associates (AM HEART J 95 187 19 8) is an outstanding contribution to the under standing of cardiac function in hypothyroidism Their results concur directionally with other data There is however a point worthy of serious dispute in the handling of systolic time intervals (STI)—namely heart rate correction of the pre-ejection period (PEP) They have chosen to correct the PEP by Weissler s regression equation

There is a large and growing body of work to show that PEP should not be rate corrected To be sure in pooled data from resting subjects an association will sometimes be found for PEP plotted against heart rate though at extremely low correlation coefficients Yet in any individual subject both atrial pacing and administration of atropine change heart rate without changing PEP Thus resting values for both heart rate and PEP are independent responses to a common factor Interventions changing heart rate alone or disproportionately would cause spurious corrected PEP changes Moreover an exaggerated rate effect could account for most or all of the PEPc correlation

In rate-correcting PEP the authors have followed a common though erroneous practice It would be helpful if they would present corresponding heart rates and uncorrected PEP values Indeed heart rates should always be given with any systolic time interval data—for completeness and for those who differ about rate correction (different investigators have different regression formulae) In my experience direc tional results for PEP and PEPc tend to be the same though at different significance levels as I am confident they would be in this otherwise exc llent work but the reader should always have the heart rate data

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Table I

	Hypothyroid		Euthyroid			Hyperthyroid	
	Without treatment	With treatment	Previously hypothyroid	Normals	Previously hyperthyroid	With treatment	Without treatment
PEP	137 5 ± 15 5 p < 0 0005	124 1 ± 15 3 p < 0 0005	92 1 ± 9 1 NS	90 7 ± 9 4	77 3 ± 13 7 p < 0 005	57 1 ± 5 6 p < 0 0005	55 0 ± 12 8 p < 0 0005
Heart rate	55 8 ± 5 5 p < 0 05	64 9 ± 7 7 NS	65 0 ± 9 6 NS	68 4 ± 13 7	76 0 ± 12 9 NS	91 8 ± 17 9 p < 0 0025	87 1 ± 19 4 p < 0 005

Data are reported as mean values ± 1 SD

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Reply

To the Editor

We are glad to furnish the data on heart rate and uncorrected preejection period (PEP) requested by Dr Spodick (see Table I)

Significance levels for uncorrected PEP are exactly the same as for corrected values ($p < 0\ 0005$) with the exception of previously hyperthyroid patients who have become euthyroid on treatment ($p < 0\ 025$ for corrected PEP vs $p < 0\ 005$ for uncorrected PEP)

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Diagnostic Electrocardiography and Vectorcardiography second edition By H Harold Friedman M D New York 1977 McGraw Hill Book Company Inc 630 pages Price $[illegible]1 00

This is the second edition of Friedman s book on electrocardiography and vectorcardiography This edition like the first is designed for the trainee as well as the practicing physician The author has simplified the approach to the understanding of the principles of ECG and VCG patterns for various types of cardiac disease states There is a lengthy and good discussion of arrhythmias which are an important aspect of heart disease The illustrations are well selected Beginners will especially profit from a study of this book The author has related the structure of the heart to the resultant ECG and VCG recordings in normal and abnormal cardiac states The legends are clearly written to explain the relatively simplified illustrations This book is worth owning and should be carefully studied in an attempt to understand the mechanisms responsible for the various tracings. VCG is now used more extensively and should be understood by those who are responsible for the interpretation of the electrocardiogram

Modern Cardiology By John Davis Cantwell M D Boston/London 1977 Butterworth & Co Ltd. 468 pages Price $[illegible]4 95

This monograph by Cantwell summarizes and interprets the cardiologic literature published since 1970 The author is in private practice and intended this book for busy practitioners who have failed to keep abreast with the medical literature as related to the practice of cardiology This is not a critical book. It represents more an interpretation of selected aspects of the literature as viewed by the author The book includes the major subjects of present interest such as exercise testing echocardiography sudden death His bundle electrocardiography and some of the new ideas concerning diagnosis pathophysiology and treatment The discussion of gallop rhythm (page 11) is an example of the new ideas presented This is an interesting book which should help the physician in clinical medicine It is well written and a good but selected bibliography is appended to each chapter All general physicians and practicing cardiologists can profit a great deal from this book designed to review the literature in cardiology for the past 5 to 6 years The book is not intended to replace other books and the literature but nevertheless this is a useful publication

Advances in Heart Disease Edited by Dan T Mason M D New York 1977 Grune & Stratton Inc 548 pages Price $34 50

This book in a series entitled Clinical Cardiology Monographs reviews the present state of concepts and knowledge of clinical cardiology The book has many contributors and is divided into seven parts which are devoted to afterload reduction therapy in congestive heart failure sudden death, acute myocardial infarction (medical and surgical management) special problems in coronary artery disease prevention and population cardiology recent advances in echocardiography and special topics in cardiovascular medicine The presentations and discussions are not critically presented to help readers who do not follow closely the literature nor are the discussions directed at bedside cardiology Some discussions have practical clinical applications whereas many do not. Twenty two of the 31 presentations are from the author s group and therefore in the main this book reflects their approach to cardiology today Clinical cardiologists will find this book to be of little value to them at present Many of the concepts are yet to be fully tested and others such as the use of glucose-insulin-potassium solution are yet to be established as of value in clinical medicine Those who study this book carefully will formulate their own opinions concerning the subjects discussed

Re-entrant Arrhythmias Mechanisms and Treatment Edited by Henri E Kulbertus, Baltimore 1977 University Park Press, 372 pages Price $39 50

This book contains the proceedings of a symposium held in Liege Belgium, during September 1976 The entire symposium was concerned with variations in the re-entrant arrhythmias. The discussions include electrophysiologic explanations for the electrocardiograms commonly seen clinically The incidence of re-entrant arrhythmias seems to be more frequent with the use of digoxin and the kaliuretic diuretics Myocardial ischemia predisposes to these arrhythmias The family physician internist and even the cardiologist will find the discussions difficult to follow even though the illustrations are well selected and clearly defined Some of the illustrations over-simplify activation of the myocardium by the wave of excitation *(see figure on page 77)* As a whole this publication should interest primarily those involved in laboratory and clinical investigation of arrhythmias. The tracings are interesting and so important in clinical cardiology that those who interpret electrocardiograms in large hospitals and clinics should study this publication carefully It is a very good book and a fine addition to the medical literature

Retrospectroscope Insights into Medical Discovery By Julius H Comroe Jr M D Menlo Park California 1977 Von Gehr Press

Julius Comroe has produced an excellent book It is fascinating to read and is full of interesting and exciting historical facts about science scientists, and the great advancements in medicine Comroe surely devoted a considerable amount of time and effort in accumulating and supporting the many facts described in his book. The over all importance of some of the advancements in physiology and biology can be debated in some instances but their introduction to medicine and clinical practice is aptly described and the important contributors are named as Dr Comroe views them This for example is well exemplified by the discussions of cardiac catheterization which is abused in many centers and hospitals throughout the world The discovery of Goodpasture in the culture of influenza virus in the chicken embryo appears to this reviewer to be the advancement which later led to viral culture on tissue culture and the polio and other viral vaccines. However these few remarks are not intended as criticisms of this very fine and interesting book but merely indicate the difficulties concerned with writing a book as important as this one The book is highly recommended to all people in the medical and scientific field It should represent an excellent gift for birth days Christmas or other occasions I found it interesting to read. This aspect of medicine and science has received too little attention Comroe rendered a good service to medicine when he produced this book It is a very good one

Books received

Principles of Cardiac Arrhythmias 2nd ed By Edward K Chung M D Baltimore 1977 The Williams & Wilkins Company 770 pages Price $49 50

Cardiac Arrhythmias Self Assessment By Edward K Chung M D Baltimore 1977 The Williams & Wilkins Company 466 pages Price $22 00

Advances in Experimental Medicine and Biology vol 82 Atherosclerosis Metabolic Morphologic and Clinical Aspects Edited by George W Manning and M Daria Haust New York 1977 Plenum Publishing Corp 1017 pages Price $75 00

Anaesthesia for Cardiac Surgery and Allied Procedures By M A Branthwaite Oxford London Edinburgh Melbourne 1977 Blackwell Scientific Publications 203 pages Price $21 50

The Cardiovascular Care Unit A Guide for Planning and Operation By Glenn O Turner M D New York Chichester Brisbane and Toronto 1978 John Wiley & Sons 512 pages

Nursing Care for Myocardial Infarction By Marilyn Rubin R.N Ph D St Louis 1977 Warren H Green 118 pages Price $10 50

Announcements

Contemporary Clinical Cardiology symposium

A two day symposium entitled Contemporary Clinical Cardiology will be held at the American Heart Association National Center in Dallas Texas on November 17 and 18 1978 The symposium is sponsored by Presbyterian Medical Center and co sponsored by the Council on Clinical Cardiology of the American Heart Association and by the Division of Continuing Education of the University of Texas Health Science Center Dallas For further information contact Presbyterian Hospital of Dallas Medical Education Office 8200 Walnut Hill Lane Dallas Texas 75231 Telephone (214) 369-4111

Cardiac Diagnosis seminar

A seminar titled Bedside Approach to Cardiac Diagnosis will be held at the Rose Medical Center Denver Colorado on December 7 and 8 1978 Sponsored by the Rose Medical Center the seminar is co sponsored by the Council on Clinical Cardiology of the American Heart Association Colorado Heart Association and by the University of Colorado Medical Center For further information contact Administrator Postgraduate Programs American Heart Association 7320 Greenville Ave Dallas Texas 75229 Telephone (214) 750 5441

First International Congress on Cardiovascular Surgery and Diseases

Drs Michael DeBakey and Eliot Corday will conduct the new world wide Congress on Cardiovascular Diseases and Surgery to be held jointly with the American Society of Contemporary Medicine and Surgery at Caesar s Palace Las Vegas Nevada on January 14 through 19 1979 Participants in the congress may receive up to 40 hours of CME credit in Category I For further information contact Dr Rutledge Howard Director of CME American Society of Contemporary Medicine and Surgery 6 N Michigan Ave Chicago Ill 60626

Cardiovascular Nuclear Medicine symposium

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American Heart Journal

December 1978 Volume 96 Number 6

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The Editors wish to express their thanks and appreciation to the following who have aided in the review of manuscripts during the past year

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Editorial

The role of acute myocardial infarction in sudden cardiac death—a statistician s nightmare

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Despite increasing evidence to the contrary the practice of attributing sudden cardiac death to an acute pathologic lesion in the heart remains widespread For example in 174 consecutive death certificates completed by doctors in Perth Western Australia in 1971 for patients who died outside hospital from coronary heart disease and did not have postmortem examinations the recorded causes of death were myocardial infarction in 72 (41 per cent) coronary occlusion in 66 (38 per cent) coronary thrombosis in 10 (6 per cent) and other causes in 26 cases (15 per cent) The true frequency of myocardial infarction on postmortem examinations of persons who have died suddenly is only 13 to 28 per cent and there is some evidence that acute coronary thrombosis only rarely precipitates the terminal event[3] The usual explanation for the paucity of acute myocardial or coronary arterial lesions at postmortem is that death has prevented the development of the inevitable pathologic abnormalities of infarction That this explanation is scientifically inept has been emphasised and recent evidence from patients who have been resuscitated from sudden death suggests that it is probably wrong Cobb and associates found that in 175 patients resuscitated from ventricular fibrillation outside hospital only about half had evidence of myocardial necrosis when subsequently studied closely in hospital In order to document the cardiac pathologic findings in a large series of sudden out of hospital cardiac deaths 500 consecutive cases which occurred in the Perth Metropolitan area between July 1973 and April 1975 were studied[7] This report deals with the 351 persons who died within half an hour of the onset of symptoms

Methods

In the Perth Metropolitan area a Coroner s autopsy is performed if the patient has not been seen by a doctor or if the attending doctor is uncertain about the cause of death Autopsies were performed by five forensic pathologists Cases were included when no pathological findings apart from those in the heart could be found to explain the cause of death Shortly after the death a member of the Western Australian Police Force carrying out routine investigations on behalf of the Coroner completed a specially designed questionnaire for the purpose of this study

Timing of deaths Precise timing of the onset of symptoms or time of death is rarely possible but in 251 cases (71 5 per cent) where death was witnessed the symptoms preceding death were known to be of less than 30 minutes duration In 100 cases (28 5 per cent) death was not witnessed but was assumed to have occurred within 30 minutes as the person had not reported symptoms or called for aid when people were constantly within earshot

Results

All cases had advanced coronary atherosclerosis Evidence of recent myocardial infarction was present in 72 cases (20 5 per cent) of these cardiac rupture was present in 24 (6 8 per

From the Departm t of Cardio scul Med cin Q ee Elizabeth II Med c l C tre Nedlands, Western Au t alia

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Editorial

The role of acute myocardial infarction in sudden cardiac death—a statistician's nightmare

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Despite increasing evidence to the contrary the practice of attributing sudden cardiac death to an acute pathologic lesion in the heart remains widespread For example in 174 consecutive death certificates completed by doctors in Perth Western Australia in 1971 for patients who died outside hospital from coronary heart disease and did not have postmortem examinations the recorded causes of death were myocardial infarction in 72 (41 per cent) coronary occlusion in 66 (38 per cent) coronary thrombosis in 10 (6 per cent) and other causes in 26 cases (15 per cent) The true frequency of myocardial infarction on postmortem examinations of persons who have died suddenly is only 13 to 28 per cent and there is some evidence that acute coronary thrombosis only rarely precipitates the terminal event The usual explanation for the paucity of acute myocardial or coronary arterial lesions at postmortem is that death has prevented the development of the inevitable pathologic abnormalities of infarction That this explanation is scientifically inept has been emphasised[5] and recent evidence from patients who have been resuscitated from sudden death suggests that it is probably wrong Cobb and associates found that in 175 patients resuscitated from ventricular fibrillation outside hospital only about half had evidence of myocardial necrosis when subsequently studied closely in hospital In order to document the cardiac pathologic findings in a large series of sudden out of hospital cardiac deaths 500 consecutive cases which occurred in the Perth Metropolitan area between July 1973 and April 1975 were studied[7] This report deals with the 351 persons who died within half an hour of the onset of symptoms

From th D partm t f C d ascul r Medicine Q ee Elizabeth II Medi l C t Nedl d Western Au tr lia
Recei ed f p t l t n No 7 1977
Reprint req ts D T Lo egr Dept. f Card asc la Med cin Q een El zabeth II Med l Cent e Nedlands Western A stralia 6009

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Methods

In the Perth Metropolitan area a Coroner s autopsy is performed if the patient has not been seen by a doctor or if the attending doctor is uncertain about the cause of death Autopsies were performed by *five forensic* pathologists Cases were included when no pathological findings apart from those in the heart could be found to explain the cause of death Shortly after the death a member of the Western Australian Police Force carrying out routine investigations on behalf of the Coroner completed a specially designed questionnaire for the purpose of this study

Timing of deaths Precise timing of the onset of symptoms or time of death is rarely possible but in 251 cases (71 5 per cent) where death was witnessed the symptoms preceding death were known to be of less than 30 minutes duration In 100 cases (28 5 per cent) death was not *witnessed* but was assumed to have occurred within 30 minutes as the person had not reported symptoms or called for aid when people were constantly within earshot

Results

All cases had advanced coronary atherosclerosis Evidence of recent myocardial infarction was present in 72 cases (20 5 per cent) of these cardiac rupture was present in 24 (6 8 per

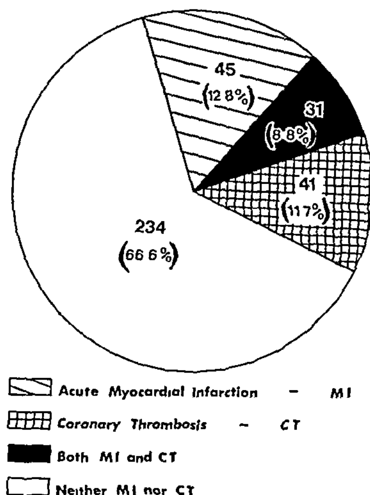


Fig 1 Pictorial presentation of 351 cases of sudden cardiac death within 30 minutes of the onset of symptoms Note that two thirds had no acute coronary or myocardial lesion

cent of total) Coronary thrombosis was found in 76 cases (21 6 per cent), and was associated with myocardial infarction in 31 (8 8 per cent of total) Thus coronary thrombosis was unassociated with infarction in 45 cases (59 2 per cent of cases of coronary thrombosis) and infarction was unassociated with coronary thrombosis in 41 (57 per cent of cases of infarction)

In 234 cases (66 6 per cent) there was no pathologic evidence of recent coronary thrombosis or myocardial infarction (see Fig 1)

Two hundred and sixty two cases (74 6 per cent) had evidence of old myocardial fibrosis and recent infarction was present in 48 of these of 89 cases without fibrosis there were 24 cases of infarction In 137 of the cases with fibrosis there was no past history of heart disease of which family or witnesses were aware

Comment

Fully two thirds of the persons in the present series of 351 sudden deaths within 30 minutes of symptoms had no acute cardiac pathologic lesion at postmortem Only one fifth had typical pathologic features of acute myocardial infarction These results from an Australian population are in line with reports on American populations[1,4] Although it cannot be known from studies of this type how many patients would have subsequently developed pathologic evidence of infarction had they survived, the traditional assumption that most would have done so is probably incorrect That most sudden cardiac deaths are due to a functional rather than structural disturbance of the myocardium and that fatal ventricular fibrillation is not necessarily due to a structural change in the myocardium is evident from experimental findings[7] and recent clinical reports[6] Conversely, many well developed myocardial infarctions which had caused no symptoms in life were identified at postmortem in this study, electrocardiographic evidence of silent infarction is a common finding in epidemiologic studies[9] The assumptions that most sudden cardiac deaths are due to early myocardial infarction and that the majority of infarctions are symptomatic are typical procrustean errors which have greatly distorted the true incidence and effects of myocardial infarction Community studies on the incidence of myocardial infarction and particularly analyses of the trends in mortality of the condition need to take account of these errors

The statistical problems of the incidence of death due to ischemic heart disease was partly recognized in the 1965 re classification of ischemic heart disease in the International Classification of Diseases,[10] where category 410 (Acute myocardial Infarction) included any acute manifestation of chronic ischemic heart disease This allowed sudden cardiac death outside hospital to be categorized under the one heading but the erroneous label of acute myocardial infarction' with its quite different connotations for clinician pathologist and epidemiologist was continued Unfortunately this confusing situation has not been corrected by the changes made in the latest (1975) revision of the Classification

An alternative term to describe sudden cardiac death does not readily present itself Terminology based on pathologic assumptions will simply perpetuate the errors described above alternative use of physiologic terms such as cardiac arrhythmia or ventricular fibrillation will be wrong when the cause of death is cardiac rupture or

acute cardiac failure The traditional term heart attack" has an attractive simplicity as has been pointed out by Sidel and colleagues [11] but its popular roots prejudice its widespread medical acceptance To overcome this problem without making any unwarranted assumptions about the mechanism of sudden cardiac death the term ischemic heart attack seems clinically pathologically and epidemiologically accurate

We wish to thank the Perth City Coroner Mr W G Wickens S M for permission to conduct this survey and for arranging facilities and accommodation to carry it out We are grateful to Dr W Laurie D S O Dr A T Pearson Dr D Hainsworth Dr J M N Hilton and Dr D A Pocock who conducted the autopsies for access to their records and for advice on technical pathology problems We thank Inspector R H Patterson for his practical help in assembling the data and Sergeant T H Bushe-Jones and the other members of the West Australian Police Force who investigated the circumstances associated with these sudden cardiac deaths and Mrs T Mason and Mrs. C Worth who carried out the secretarial work.

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Clinical communications

Radionuclide assessment of ventricular performance during propranolol withdrawal prior to aortocoronary bypass surgery

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Propranolol s antianginal effects are believed to be due predominantly to its reduction in myocardial oxygen consumption secondary to inhibition of the positive chronotropic and inotropic actions of catecholamines However, this decrease in adrenergic support could exacerbate regional and global ventricular dysfunction and precipitate congestive heart failure Clinical studies on the effects of propranolol on left ventricular performance have yielded conflicting results After intravenous administration of propranolol, a consistent negative inotropic effect at the time of cardiac catheterization has not been documented [1 3] Recently, Shubrooks and colleagues[4] failed to demonstrate a significant change in ejection fraction or regional wall motion following this mode of propranolol administration Echocardiographic functional assessment also has been variable after oral administration While some studies have shown no effect, others have demonstrated a depression in ejection fraction and posterior wall motion in patients with angina pectoris [5 6] However, this approach is not optimal for study of patients with coronary artery disease because the assumptions required for echocardiographic calculation of ventricular volumes are not valid in the presence of regional wall motion abnormalities [7]

Newly developed radionuclide techniques for evaluation of ventricular performance in coronary artery disease may offer significant advantages over contrast angiography and conventional M mode echocardiography With first pass quantitative radionuclide angiocardiography analysis is based upon radionuclide time-activity curves and consequently is independent of the geometric assumptions inherent in volume determinations made from outlines of cavitary silhouettes [8 12] Reproducible first pass techniques with minimal variability have been developed and validated in this laboratory [1 11]

The present study was undertaken to assess the net inotropic effects of oral propranolol upon left ventricular performance Preoperative patients receiving chronic propranolol therapy for angina pectoris were studied during drug withdrawal This situation was felt to represent a commonly encountered clinical model in which drug effects could be studied Left ventricular ejection fraction mean normalized ejection rate and regional

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This study was supported in part by National Heart Lung and Blood Institute Contract N01HV52977 and National Heart Lung and Blood Institute Grant R01HL21690-01

Received for publication Dec 29 1977

Accepted for publication Feb 1 1978

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wall motion were determined using first pass radionuclide angiocardiography on multiple occasions as propranolol was tapered prior to elective aortocoronary bypass surgery

Methods

Patient population The study population consisted of 18 preoperative patients with documented coronary artery disease and clinically stable angina pectoris All patients underwent left and right heart cardiac catheterization coronary angiography and left ventriculography Seventeen patients had significant (> 70 per cent) stenosis of at least two coronary arteries one patient had significant single vessel disease Sixteen patients were male and two female with a mean age of 52 years (range 34 to 65 years) Ten patients had both clinical and electrocardiographic evidence of previous myocardial infarction Infarcts were transmural in five patients (defined by Q waves 0 04 sec in duration) and non transmural in five patients (defined as persistent T wave inversions)

At the time of admission for surgery all patients had been on propranolol therapy for at least one month There was no change in the propranolol dosage for at least two weeks prior to admission Two patients were receiving digoxin therapy for congestive heart failure Fourteen patients were receiving long acting nitrates two patients were receiving diuretics At the time of referral for surgery ten patients had New York Heart Association Class III angina and eight had Class II angina Informed consent was obtained from each patient

Excluded from the study population were (1) patients with unstable angina defined as recurrent pain at rest with associated ST segment or T wave changes (2) patients in whom intraaortic balloon counterpulsation therapy was initiated preoperatively and (3) patients with significant valvular heart disease

Radionuclide technique and serum propranolol assay Following preoperative hospital admission three radionuclide angiocardiograms were performed in each patient The first study was obtained at each patient s maximal propranolol dose (mean ± SEM 224 ± 29 mg /day range 160 to 640 mg /day) The second study was obtained 24 to 48 hours later at an intermediate propranolol dose (99 ± 9 mg /day range 80 to 160 mg /day) and the third study was obtained at least 24 hours following discontinuation of propranolol Studies were performed two to three hours after an oral dose of propranolol The drug was administered at six hour intervals All patients receiving nitrates or digitalis continued on their normal dosage regimen during propranolol withdrawal Digitalis was administered orally at least 6 hours prior to each study Nitrates were administered sublingually at least 3 hours prior to evaluation

All radionuclide studies were performed in a Cardiovascular Nuclear Imaging Laboratory An 18 gauge 1½ polyethylene catheter was placed in an antecubital vein for injection of radionuclide and for withdrawal of blood samples needed for determination of serum propranolol levels Following venipuncture five to ten minutes were allowed to pass to minimize any possible contributions of sympathetic activity associated with the procedure Prior to each radionuclide study heart rate and blood pressure were recorded Ten ml of blood were withdrawn into glass syringes and centrifuged for 10 minutes The serum was frozen and maintained at 0° C until propranolol levels were determined by the fluorometric method of Shand and colleagues[14] The sensitivity of this assay has been determined to be ± 5 ng /ml

Radionuclide angiocardiograms were performed with patients supine in the anterior position using a commercially available computerized multicrystal scintillation camera (Baird Atomic System 77 Bedford Mass)[1] Briefly 15 to 20 mCi of technetium 99m pertechnetate dissolved in less than 1 ml of normal saline were injected rapidly and flushed with 20 ml of saline Data were acquired in frame mode at 50 msec intervals for 20 seconds as the bolus of tracer initially passed through the central circulation A high frequency time–activity curve was generated from a left ventricular region of interest (Fig 1) End diastolic frames were used as starting points to sum together counts at 50 msec intervals over three to five cardiac cycles forming a summed cardiac cycle A series of background frames (equal to the number of cardiac cycles used) was selected from the left ventricular time–activity curve just prior to the first discernible left ventricular beat The sum of the background frames was subtracted from the summed cardiac cycle forming a high count rate background corrected representative cardiac cycle



Fig 1 High frequency high count rate time-activity curve used to calculate left ventricular ejection fraction in a normal patient *Each peak and valley* represent one cardiac cycle

This is equivalent to a relative ventricular volume curve Left ventricular ejection fraction was calculated directly from these data according to the formula

Ejection fraction = End diastolic counts − End systolic counts/End diastolic counts/ × 100

Ejection fraction determined in this manner has been shown to correlate closely with data obtained using standard contrast angiographic techniques for calculation of ejection fraction [12]

In addition, normalized mean ejection rate was determined from the same "representative cycle Counts during the ejection phase were fitted to a weighted least squares straight line and the slope of this line (dC/dt) was normalized to the average counts (C) during the ejection phase yielding dC/dt C Left ventricular ejection rate is analogous to dV/dt of the ventricular volume curve and has been found to be sensitive to pharmacologic changes in inotropic state [12]

Assessment of left ventricular wall motion was determined from analog end diastolic and end systolic images also obtained from the representative cycle Images were computer smoothed by expanding the 294 matrix points to 4,704 points using a five point linear extrapolation A computer generated ring representing the end diastolic outer margin was superimposed upon the end systolic image (Figs 2 and 3) Regional wall motion was evaluated from this composite image and was considered normal hypokinetic or akinetic In the anterior position the left ventricular silhouette was divided into anterolateral apical inferior and posterobasal segments Regional wall motion was evaluated by two observers, and the consensus was used in data analysis Previous work in this laboratory has demonstrated excellent agreement between analyses determined by this technique and contrast angiography [1]

The variability of these radionuclide parameters has been previously determined by multiple, sequential studies in 20 stable control patients with both normal and abnormal baseline left ventricular performance For left ventricular ejection fraction, variability averaged (± SD) 4 4 ± 3 6 per cent with comparable differences in both patients and normal and abnormal left ventricular performance In the same study, left ventricular ejection rate had an intrinsic variability of 0 56 ± 47 sec [1] Furthermore, variability was greater in those patients with normal left ventricular performance The presence or magnitude of regional wall motion abnormalities also did not change from study to study [13]

Statistical analysis Data are expressed as the mean ± standard error (SEM) Comparisons between studies in individual patients were made with a paired t test

Results

Indices of left ventricular performance There was no significant change in left ventricular ejection fraction measured on the three occasions during propranolol withdrawal (59 1 ± 2 4 per cent vs 60 4 ± 2 0 per cent vs 59 2 ± 2 5 per cent $p > 0.05$) (Fig 4) Five of 18 patients had mildly to moderately abnormal ejection fraction (range 43 to 48 per cent) In this subgroup as well ejection fraction did not change significantly as propranolol was withdrawn In the total group two patients demonstrated an increase and four a decrease in ejection fraction beyond the intrinsic variability of the technique from initial to final studies Individual patients varied from 0 to 10 per cent during the study period (greatest increase in ejection fraction 8 per cent greatest decrease in ejection fraction 10 per cent)

Normalized left ventricular ejection rate also did not change significantly as propranolol was

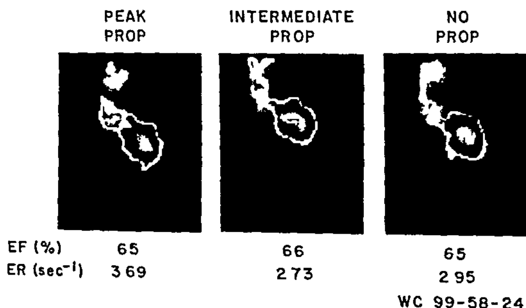


Fig 2 Serial regional wall motion studies in patient E M obtained in the anterior position In each image *the outer ring* represents the computer generated end-diastolic perimeter and *the image within the ring* represents end systole Note the normal wall motion in each study Ejection fraction *(EF)* and ejection rate *(ER)* are given below each image *PROP* = propranolol

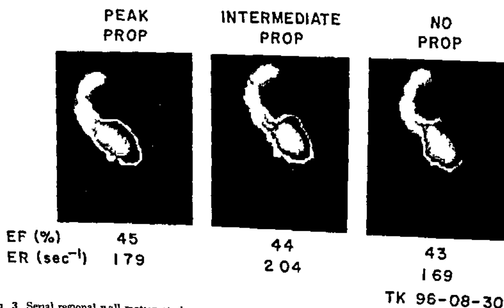


Fig 3 Serial regional wall motion studies in patient T K Note the posterobasal hypokinesis in each study Abbreviations as in *Fig 2*

withdrawn (2 80 ± 18 sec vs 2 87 ± 18 sec vs 2.92 ± 0 20 sec p > 0 05) This was a consistent finding both in patients with abnormal (< 2 50 sec) and normal initial ejection rates Four patients demonstrated increases and two decreases in ejection rate from initial to final studies beyond the intrinsic variability of the radionuclide technique Individual patients varied from 0 10 to 1 63 sec ¹ during the study period (greatest increase in ejection rate 1 63 sec ¹ greatest decrease 0 99 sec ¹) (Fig 5) The greatest lability in ejection rate was noted in patients with normal left ventricular performance The degree of variation was comparable to

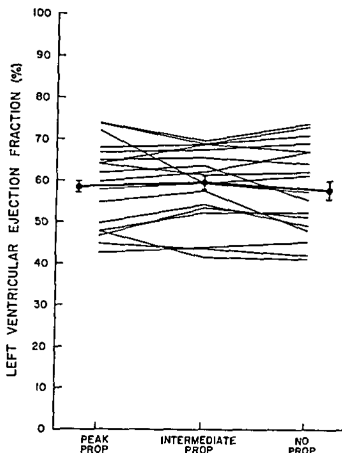


Fig 4 Sequential measurements of left ventricular ejection fraction in 18 patients studied as propranolol *(PROP)* was tapered preoperatively Data in each individual patient are represented *by the thin solid lines* Mean values for the entire group are *shown by the circles connected by the heavy solid line* *Vertical bars* represent standard errors *NS* = not significant by paired t test

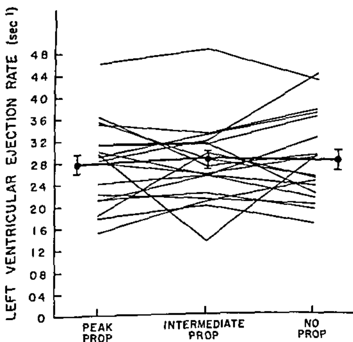


Fig 5 Sequential measurements of left ventricular ejection rate in 18 patients The format and abbreviations as in *Fig 4*

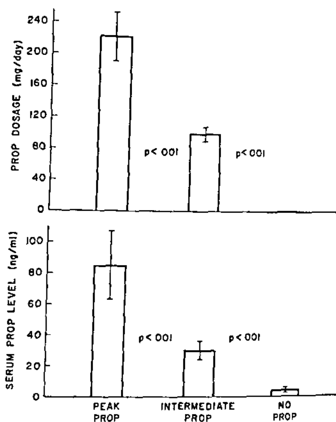


Fig 6 Mean ± SEM daily propranolol dosage for the three studies *(Top)* and Mean ± SEM serum propranolol levels at the time of peak intermediate and final studies *(Bottom)* Note the significant decrease in serum levels at the intermediate and final studies in comparison to peak level

that seen in normal, stable control patients[13]

In six patients radionuclide regional wall motion was abnormal at Study 1 Three patients demonstrated akinesis and three hypokinesis of a left ventricular segment These regional wall motion abnormalities were in close agreement with those assessed by preoperative contrast left ventricular angiography There was no observable change in the magnitude or extent of regional wall motion abnormalities as propranolol was withdrawn in these six patients Furthermore, no patient developed new abnormalities in regional wall motion during drug withdrawal and all patients with normal initial performance remained normal on subsequent studies Two patients with anterior hypokinesis at left ventriculography demonstrated normal left ventricular regional wall motion with radionuclide angiography

Serum propranolol levels Serum propranolol levels significantly decreased as propranolol was withdrawn and were virtually not detectable at the time of the final study (Fig 6) The peak propranolol level at Study 1 averaged 85 ± 22 ng/ml, with a range from 15 to 371 ng/ml

Intermediate study propranolol levels averaged 30 ± 6 ng/ml with a range from 5 to 81 ng/ml Serum propranolol levels at the final study averaged 4 ± 2 ng/ml

Heart rate systolic blood pressure Heart rate increased significantly ($p < 0.001$) during preoperative propranolol withdrawal from 62.3 ± 2.3 to 67.8 ± 3.0 to 73.1 ± 2.3 beats/minute The increase in rate changed from 0 to 20 beats/minute Changes in heart rate were similar in patients with normal ejection fraction (11 beats/minute) and abnormal ejection fraction (10 beats/minute) Mean systolic blood pressure was not altered significantly (114.7 ± 4.3 vs 110.3 ± 3.0 vs 113 ± 3.0 mm Hg $p > 0.05$) as the propranolol dosage was reduced

Discussion

This study demonstrates that in patients with documented coronary artery disease preoperative propranolol withdrawal does not result in significant modification of basal global and regional left ventricular performance The clinical situation of preoperative propranolol withdrawal provided a suitable model for study since all patients received clinically relevant drug dosages all were observed in a controlled hospital environment and all had documented coronary artery disease The technique of quantitative first pass radionuclide angiocardiography provided a good method of study since it is independent of ventricular geometry and correlates well with contrast angiographic data in patients with and without coronary artery disease Furthermore sequential data have been obtained with low variability indicating the suitability of the method for this type of investigation [3]

Several studies have demonstrated significant negative inotropic effects following intravenous propranolol administration [1,15,16] However questions still remain concerning the effect of chronic oral propranolol therapy upon ventricular performance in the basal state in man The conflicting results of some previous studies may be due to the nature of the noninvasive techniques employed Employing roentgenographic left heart dimensions and systolic time intervals in normal subjects Le Winter and colleagues did not demonstrate any change in cardiac dimensions or the ratio of pre ejection period to left ventricular ejection time following oral propranolol In contrast Frishman and associates[8] found a reduction in echocardiographic ejection fraction and posterior wall motion in patients with angina following therapy with propranolol However these echocardiographic techniques for the evaluation of ventricular performance have been found to be unreliable in the patient with coronary artery disease and regional ventricular dysfunction On the other hand this is clearly not the case with the radionuclide techniques used in the present study for assessment of ejection fraction The contrasting efficacy of the two techniques in patients with coronary artery disease has been reported by Henning and co workers[18] who showed a poor correlation between echocardiographic and radionuclide ejection fraction in patients with regional wall motion abnormalities

Ejection fraction is the most commonly used clinical parameter of global left ventricular performance However it is dependent upon variables other than intrinsic myocardial contractility such as heart rate preload afterload and the presence of valvular regurgitation [19] Thus studies demonstrating changes in ejection fraction following propranolol must be interpreted in light of simultaneous alterations in these parameters as well In the present study systolic blood pressure an approximate index of afterload did not change significantly as propranolol was withdrawn However there was an increase in heart rate noted during propranolol withdrawal Although this heart rate change did not affect ejection fraction it may have resulted in concomitant alterations in both end diastolic and end systolic volumes

There is wide variation in the dosage of propranolol required for clinical relief of angina [20] In part this may be due to marked differences in sympathetic tone from one patient to another However in the basal state beta adrenergic support to left ventricular function is probably minimal The most commonly used clinical criterion for determining adequacy of dosage is reduction of the resting pulse usually to 50 to 60 beats/minute This was the heart rate response most frequently encountered in patients in this study all were felt to have received maximal or close to maximal beta blocking therapy for angina by their referring physicians

Although serum propranolol levels also demonstrate wide variability serum levels of 50 to 100 ng/ml are regarded nevertheless as indicating a

significant degree of beta blockade[21] Pine and colleagues[22] suggested that maximal beta blockade to endogenous stimuli occurs at serum levels of 100 ng/ml In the present study, the peak dosage of 224 ± 27 mg/day and corresponding serum levels of 85 ± 22 ng/ml may not represent maximal beta blockade but are compatible with a significant drug effect and are values commonly encountered in clinical practice

Several studies have demonstrated a temporal disparity between serum propranolol levels and the degree of beta blockade Faulkner and associates[3] could not detect propranolol in the plasma or left atrial tissue obtained from patients undergoing bypass surgery in whom propranolol had been withdrawn 36 to 48 hours earlier Furthermore the norepinephrine sensitivity of left atrial tissue obtained from these patients did not significantly differ from control patients Romagnoli and Keats[24] assessed the effects of isoproterenol infusion on patients with coronary artery disease 18 hours after withdrawl of chronic oral propranolol therapy There was no significant difference in heart rate response between the propranolol treated group and a control group with coronary artery disease Leaman and co workers[1] failed to demonstrate any depression of heart rate, cardiac output, or triple product 36 hours following discontinuation of oral propranolol The difficulties in relating the magnitude of beta blockade to serum propranolol levels following oral administration are further compounded by the presence of metabolites such as 4 hydroxypropranolol which also have beta blocking properties[0]

It is conceivable therefore that in the present study while plasma propranolol levels at the final measurement were virtually undetectable there were residual beta blocking effects present at the time of this study Nevertheless the significant decrease in propranolol levels and concomitant increase in heart rate suggests that a substantial reduction in the effects of propranolol had occurred during the study period The results of the present study are similar to those of Marshall and colleagues[5] who sequentially assessed the effects of increasing oral propranolol dosage upon left ventricular performance in patients with stable angina or ventricular arrhythmias Increases in dosage occurred at intervals of at least 48 to 72 hours While propranolol levels significantly increased and heart rate declined, there was no significant change in left ventricular ejection fraction, ejection rate or regional wall motion noted

It must be emphasized that the majority of the patients in this study had normal ventricular function Only six had regional wall motion disturbances and five had abnormal ejection fraction The effects of propranolol upon basal ventricular performance in the patient with more pronounced intrinsic myocardial dysfunction may differ considerably from those observed in the present study Coltart and co workers[1] noted adverse effects of intravenous propranolol only in those patients with preexisting severe myocardial dysfunction Two patients with anterior wall hypokinesis at left ventriculography demonstrated normal regional wall motion with radionuclide angiography It is possible that subtle changes in regional wall motion induced by propranolol in these two patients may be beyond the current resolution of the radionuclide technique employed However, since contrast angiographic and radionuclide studies were separated by several months direct comparison of these two studies may not be valid in these patients

Two points require additional emphasis The present study was performed in the basal state No statement can be made concerning the response of the left ventricle to stress in a patient receiving propranolol This has particular relevance to the clinical question of propranolol withdrawal prior to cardiac surgery Although ventricular performance was unchanged in these patients preoperatively, responses to anoxic or ischemic stress or the effects of prolonged cardiopulmonary bypass might be quite different Finally the situation of acute myocardial infarction and sudden death developing during abrupt preoperative propranolol withdrawal has been reported[26] Although this study does not address that clinical question the data would indicate that the major change in resting myocardial oxygen requirements during propranolol withdrawal results from an increase in heart rate rather than from major changes in global or regional left ventricular pump performance

Summary

The effects of oral propranolol upon left ventricular performance were assessed in 18 patients with angiographically documented coronary artery disease in whom propranolol was

tapered prior to elective aortocoronary bypass surgery Left ventricular ejection fraction ejection rate and regional wall motion were obtained on three occasions with first pass radionuclide angiocardiographic techniques Patients were studied at peak propranolol dose (± SEM) 224 ± 29 mg/day serum propranolol level 85 ± 22 ng/ml) intermediate dose (99 ± 9 mg/day serum propranolol 30 ± 6 ng/ml) and 24 hours following discontinuation of propranolol therapy

Heart rate increased significantly (62 ± 2 3 vs 67 ± 3 0 vs 73 ± 2 3 beats/minute $p < 0\,001$) during propranolol withdrawal while systolic blood pressure did not change significantly (114 7 ± 4 3 vs 110 3 ± 3 0 vs 113 ± 3 0 mm Hg $p > 0\,05$) There was no significant change in ejection fraction (59 1 ± 2 4 vs 60 4 ± 2 0 vs 59.2 ± 2 5 per cent) or ejection rate 2 60 ± 0 18 vs 2 87 ± 0 18 vs 2 92 ± 0 20 sec) as propranolol was tapered ($p > 0\,05$) No patient demonstrated a change in regional wall motion in response to propranolol withdrawal The results of this study suggest that oral propranolol in commonly used clinical dosages does not significantly affect radionuclide measures of left ventricular performance in the basal state

We thank Dr Ronald Leonardi of Ayerst Laboratories New York N Y for obtaining the serum propranolol assays as well as Ms. Linda Pytlick for technical assistance and Ms Coletta Sawyer for secretarial assistance

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Electrophysiological studies in four patients with atrial flutter with 1:1 atrioventricular conduction

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Atrial flutter with sustained 1:1 atrioventricular (AV) conduction is an uncommon dysrhythmia which normally causes serious hemodynamic disturbance. It may develop as a result of treatment of atrial flutter with drugs which can accelerate AV conduction such as quinidine, procainamide, atropine, and phenytoin sodium. It has been described as an uncommon complication in patients with pre-excitation syndromes, particularly during electrophysiological study,[1,2] but has also occasionally been documented as occurring spontaneously in patients without obvious evidence of pre-excitation, in some of whom the arrhythmia may have been precipitated by factors increasing sympathetic tone such as physical or emotional stress, induction of anaesthesia, or thyrotoxicosis. Castellanos and co-workers have suggested that patients manifesting atrial flutter with spontaneous 1:1 AV conduction may have partial AV nodal bypass tracts, and this postulate has been supported by electrophysiological studies in one such patient reported by Aranda and colleagues. To investigate this hypothesis further, we have performed electrophysiological studies in four patients with no electrocardiographic evidence of pre-excitation who developed atrial flutter with spontaneous 1:1 AV conduction.

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Received for publication Jan. 12, 1978.
Accepted for publication Feb. 2, 1978.
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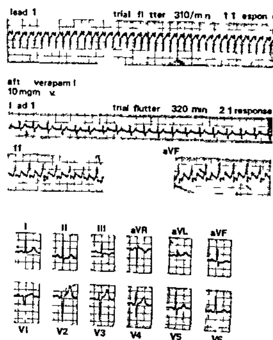


Fig. 1. Electrocardiograms of Case 1 during atrial flutter with 1:1 and 2:1 AV conduction and following conversion to sinus rhythm (12-lead ECG).

Patients and methods

Patient selection. An electrocardiographic diagnosis of atrial flutter with 1:1 AV conduction was made in patients with a regular tachycardia exceeding 230 per minute without evidence of AV dissociation, in whom the atrial rate could be shown to be unchanged during second degree AV block when present in the previous or subsequent electrocardiogram, and in whom the QRS morphology when in sinus rhythm was similar to that seen during the tachyarrhythmia.

These criteria were fulfilled in four patients, in

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Table 1 Clinical data

Patient No	*Sex & age*	*Presentation*	*ECG during tachyarrhythmia*	*Comment*
1	Male 26	Angina effort dyspnea and palpitations for 2 months Right basal pneumonia	Atrial flutter 310/min with 1 1 AV conduction QRS width 0 08 sec 2 1 AV conduction after verapamil (Fig 1)	Studied ?0 months after presentation No recurrence of arrhythmia Off therapy for 19 months
?	Male 53	Episodic palpitations for 1 year Angina and dyspnea with palpitations for 3 weeks	Atrial flutter 290/min with 1 1 AV conduction QRS width 0 12 sec (RBBB) Variable ? AV block after verapamil (Fig 2)	Studied 15 months after presentation No recurrence of arrhythmia Off therapy for 6 months
3	Male 53	Symptoms of hyperthyroidism palpitations with angina and sweating for 5 months	Atrial flutter 290/min with 1 1 AV conduction QRS width 0 09 sec Variable 2 AV block after verapamil and practolol (Fig 3)	Studied 3 years after presentation No recurrence of symptoms after treatment of thyrotoxicosis with I
4	Male ?8	Recurrent palpitations and dizziness for 7 years Sick sinus syndrome with 1 AV block Left axis deviation and intraventricular conduction disturbance Congestive cardiomyopathy	Atrial flutter 40/min with 1 1 AV conduction QRS width 0 18 sec Atrial flutter ?40/min with variable 2 AV block after digitalization (Fig 4)	Studied 2 months prior to presentation with atrial flutter and 1 1 AV conduction

of study A tripolar electrode catheter was introduced percutaneously via the right femoral vein to record the His bundle electrogram as described by Scherlag and co workers[6] and a quadripolar electrode catheter (inter electrode distance 1 cm) introduced by the same route was positioned along the lateral border of the right atrium The distal pair of electrodes was used to stimulate the right atrium and the proximal pair to record a right atrial electrogram Standard electrocardiographic Leads I II III VI and V and intracardiac electrograms were recorded at a paper speed of 100 mm/sec using an eight channel direct writing ink jet recorder* Electrical stimulation from the mid right atrium was performed for 60 second periods at progressively higher rates until second degree AV block developed Recordings were made during the last 30 seconds of each period and time was allowed between each pacing period for the rhythm to return to the control rate The refractory periods of the AV conducting system were then measured by the extrastimulus method * Using a Medtronic SP 1349A pulse generator* the right atrium was paced at a cycle length slightly less than that of the sinus node and premature atrial impulses of 2 msec duration and approximately twice diastolic threshold were introduced after every eighth paced beat The coupling interval of the premature atrial impulse was reduced by 5 to 10 msec decrements until the atrium became refractory In three patients repeated studies were performed at shorter paced atrial cycle lengths After completion of these baseline measurements three of the four patients received 0 75 mg strophanthin intravenously (IV) over a period of approximately 15 minutes and both atrial pacing and atrial premature stimulation studies were repeated after 20 to 70 minutes

Definition of terms Standard definitions and normal values for AV conduction times (PA 27 ± 18 msec AH 92 ± 38 msec HV 43 ± 12 msec) were used[10]

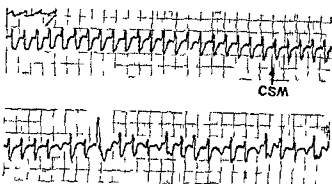
The maximal pacing rate was defined as the highest atrial pacing rate at which consistent 1 1 AV conduction could be maintained

The pacing range was defined as the difference between the minimal and maximal atrial pacing rates per minute for each pacing study

The Δ AH was defined as the difference between the AH intervals at the maximal and minimal atrial pacing rates

*Elema Schonander Stockholm Sweden

lead 11 atrial flutter 290/min 1 1 response



after verapamil 15mg IV
atrial flutter 290/min with irregular ventricular response

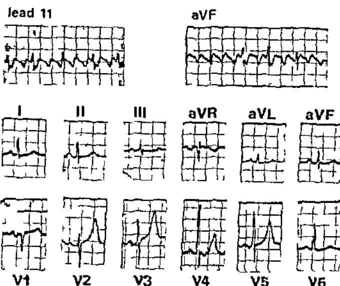


Fig 2 Electrocardiograms of Case 2 Upper three panels show continuous rhythm strips during atrial flutter with the development of varying second degree AV block during carotid sinus massage *(CSM)* and subsequently after intravenous verapamil Note wide QRS complexes during atrial flutter *Lower two panels* show 12 lead ECG following conversion to sinus rhythm

three of whom electrophysiological studies were performed 15 months to 3 years after atrial flutter with 1 1 AV conduction had first been documented In the fourth patient the electrophysiological study had been performed because of an undiagnosed tachyarrhythmia 2 months prior to documented atrial flutter with 1 1 AV conduction

Clinical details of the four patients are summarized in Table I and their ECG s both during atrial flutter with 1 1 AV conduction and during sinus rhythm are shown in Figs 1 to 4 It should be noted that none of the four patients had abnormally short PR intervals nor delta waves to suggest pre excitation on their 12 lead ECG during sinus rhythm

monitor lead

atrial flutter 290/min
1 1 response

after verapamil & practolol IV
monitor lead atrial flutter 290/min 2° AV block

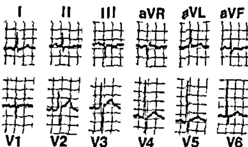


Fig 3 Electrocardiograms of Case 3 during atrial flutter with 1 1 conduction and varying second degree AV block and following conversion to sinus rhythm (12 lead ECG)

lead 11 atrial flutter 240/min 11 response

after digoxin

lead 11 atrial flutter 240/min 2 AV block

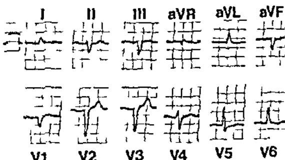


Fig 4 Electrocardiograms of Case 4 during atrial flutter with 1 1 conduction and varying second degree AV block and following conversion to sinus rhythm (12 lead ECG) Note wide QRS complex during atrial flutter with 1 1 conduction

Methods Informed consent was obtained from all patients for intracardiac electrophysiological studies which were performed using local anesthesia in the postabsorbtive non sedated state No patient was taking cardioactive drugs at the time

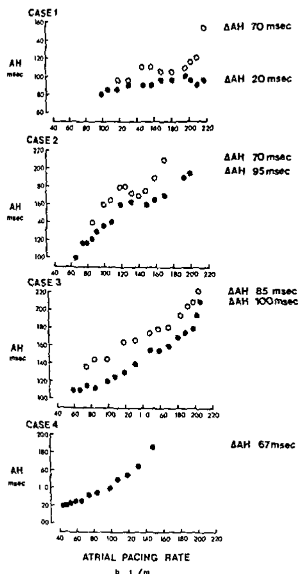


Fig 5 Graphic representation of changes in AH intervals at increasing atrial pacing rates during 1 1 AV conduction in each of the four cases both in the control state *(closed circles)* and following intravenous strophanthin *(open circles)* ΔH = total increase in AH interval (msec) over the range of pacing rates

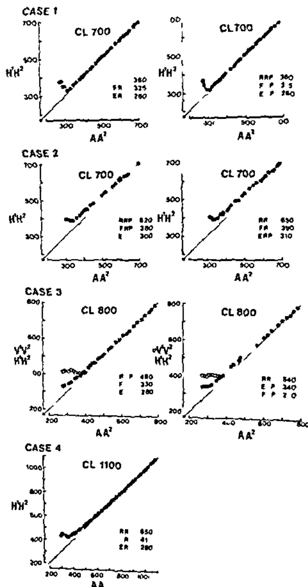


Fig 6 AV function curves derived from extrastimulus studies during paced atrial rhythm *(CL = cycle length)* in each of the four cases Studies performed in the control state are shown *on the left hand panels and those following* intravenous strophanthin *on the right* In each panel A A coupling intervals are plotted on the abscissa and H H *(closed circles)* and V V *(open circles)* on the ordinate

increasing rates of atrial pacing In Cases 2 and 3 there was no significant change in the ΔAH or AH gradients after intravenous strophanthin In Case 1 however the ΔAH was abnormally short (20 msec) with an AH gradient of only 17 in the control state but after intravenous strophanthin the ΔAH and AH gradients increased to values of 70 msec and 71 respectively These increases were largely due to a sudden increase in the AH interval only at maximal atrial pacing rates

Refractory periods For each patient the refractory periods of the atrium AV node and ventricular specialized conducting system as determined by the extrastimulus technique are summarized in Table III Representative AV function curves both before and after intravenous strophanthin from which the AV refractory periods were measured are illustrated in Fig 6

The atrial functional refractory period in the

Table II AV conduction times and results of atrial pacing

	AV conduction times (msec)					*Atrial pacing data*			
Case No	*Sinus cycle length*	*PA*	*AH*	*HV*	*PR*	*Maximal pacing rate (beats/min)*	*Pacing range (beats/min)*	*Δ AH (msec)*	*AH gradient*
1	735	20	95	45	160	C 218	118	20	17
						D 218	98	70	71
2	955	30	105	50	185	C 200	134	95	71
						D 171	85	70	82
3	1005	15	130	50	185	C 207	147	100	68
						D 207	132	85	64
4	—*	30	145	85	260	C 150	105	67	64

C = control D = following IV strophanthin
Pacing range = difference between minimal and maximal atrial pacing rates per minute
= junctional rhythm with occasional non consecutive sinus beats

The AH gradient was obtained by dividing the Δ AH interval by the pacing range in each study

The functional refractory period of the atrium was defined as the shortest attainable interval between two successive atrial depolarisations (A' A) The relative refractory period (RRP) of the AV node was defined as the longest A' A interval at which H' H was longer than A' A

The functional refractory period (FRP) of the AV node was defined as the shortest interval between two successive His bundle responses propagated from the atrium

The effective refractory period (ERP) of the AV node was defined at the longest A' A² interval that failed to conduct to the bundle of His

Results

AV conduction times Three of the four patients were in sinus rhythm at the time of study and showed normal PR intervals and AV conduction times (Table II) The fourth patient was cardioverted at the beginning of the study from atrial tachycardia (210/minute) conducted with 2 1 AV block to an unstable junctional rhythm (mean ventricular rate 43/minute) with intermittent episodes of sinus bradycardia and escape capture bigeminy Both AH and HV times were prolonged

Atrial pacing In three of the four patients the maximal rate of pacing at which 1 1 AV conduction was maintained was determined before and after IV strophanthin In these patients the control values were in excess of 200/minute (range 200 to 218/minute) (Table II) These rates although fast, were considerably slower than the maximal rate at which 1 1 conduction occurred spontaneously during atrial flutter Although intravenous strophanthin significantly prolonged the AH interval at any particular pacing rate in all three cases (Fig 5), it reduced the maximal pacing rate achieved in only one of the three (Case 2) In the fourth patient Wenckebach AV block developed at atrial pacing rates above 150/minute and in this patient the effect of intravenous strophanthin was not assessed

The results of atrial pacing were also analyzed by plotting AV nodal conduction times (AH intervals) against the rate of pacing both in the control state and after intravenous strophanthin (Fig 5) As has been shown in normal subjects by Scherlag and colleagues,[11] the AH interval increased almost linearly with increasing pacing rates in three of the four patients The total increase (ΔAH) was expressed as a function of the pacing range to give a figure representing the gradient of the AH response to rapid atrial stimulation (AH gradient) To obtain normal values AH gradients were calculated from two previously reported studies comprising 24 apparently normal subjects with normal PR intervals *in* whom Wenckebach AV block did not develop at pacing rates less than 120/minute[11, 12] In these patients values for ΔAH ranged from 35 to 160 msec and AH gradient varied from 29 to 2 76 (mean ± SD = 1 31 ± 0 63)

In Cases 2 3 and 4 the control values for ΔAH with AH gradients (Table II) fell within the above normal ranges indicating *a normal* increase in AV nodal conduction time with

were significantly prolonged following ouabain The authors concluded that these results were compatible with either a partial AV nodal bypass or an AV node with unusual capacity for rapid conduction

In this study we were faced with a similar difficulty in interpretation of the data because of limited data on normal values for the responses of AV conduction to atrial pacing and for AV nodal refractory periods In adult patients without clinical or electrocardiographic evidence of AV nodal disease previous investigators have shown that the atrial pacing rate at which Wenckebach AV block first developed ranged from (mean ± SD) 150 0 ± 24 2 to 170 2 ± 26 8 beats/minute with two of the four patients studied by Reddy and associates [4] showing 1 1 AV conduction to rates of 200/minute That this is an age related phenomenon has been demonstrated by Pahlajani and colleagues [18] who showed that 9 of 13 children under the age of 13 years developed Wenckebach AV block at atrial pacing rates only in excess of 200/minute and that under the age of 3 years 1 1 AV conduction at rates in excess of 250/minute was common It has been suggested by these authors that adults manifesting 1 1 AV conduction at very rapid rates may have immature AV nodes without bypass tracts Although three of the four patients in this study manifested 1 1 AV conduction at rates in excess of 200/minute in none did the rate at which Wenckebach AV block developed during paced atrial rhythm approach the maximum ventricular response achieved during spontaneous atrial flutter A similar contrast between the rate at which 1 1 AV conduction occurred during atrial pacing and that occurring spontaneously or induced by exercise has been observed previously [7] and has been attributed to the conduction delay in the nodal tissues produced by pacing induced liberation of acetylcholine

The limits of normality for incremental change in AH interval with atrial pacing at increasing rates are not well defined Caracta and colleagues quote an average normal value for ΔAH of 120 msec without tabulating the original data Comparing the results in our four patients with those of two series of adults without ECG evidence of AV nodal disease or pre excitation in whom suitable data on the normal response to atrial pacing is available [2] only one patient (Case 1) demonstrated an abbreviated increase in the AH interval during atrial pacing (ΔAH = 20 msec AH gradient = 17) suggesting the possibility of a partial AV nodal bypass

In assessing the results of the extrastimulus studies in these patients the problem of definition of the normal values again arises particularly in view of the evidence that AV nodal refractory periods in man are both rate and age dependent [1, 2] Comparison of the data for AV nodal refractory periods in this study with that of five previous studies which have examined these parameters in normal subjects at similar driven cycle lengths [1] showed that the values for FRP and ERP of the AV node in all four patients were within these normal limits Only the AV nodal RRP in Case 1 appeared unusually short

We conclude that a partial AV nodal bypass could explain the 1 1 ventricular response during atrial flutter in Case 1 However no evidence for an AV nodal bypass tract could be found in the remaining three cases Other possible explanations include alteration in sympathetic tone during prolonged attacks of atrial flutter affecting the conduction properties of the AV node [5] or alteration in the AV nodal functional refractory period with continuous and prolonged rapid atrial stimulation during atrial flutter A different route of entry of the wavefront into the AV conducting system during atrial flutter could have influenced the properties of the normal AV node thus explaining discrepancies between the ventricular rate during atrial flutter compared to that observed during high right atrial overdrive pacing Janse s [3] animal work showed how the site of atrial stimulation could influence the route of entry of the atrial wavefront and hence the conduction properties of the AV node Clinical studies also have shown the effects of varying the site of atrial pacing on AV nodal refractory periods ΔAH and AH gradients [1, 21] The case reported by Aranda and colleagues[7] in whom dual AV nodal pathways were demonstrable during pacing from the high right atrium or coronary sinus but not from the mid right atrium suggests that access to an AV nodal bypass tract could have been denied to impulses arising from the sinus node or during high right atrial overdrive pacing but not during atrial flutter in Cases 2 3 and 4 This has not however been described thus far in the presence of a normal PR interval on the resting electrocardiogram and seems less likely Without studies of AV conduction from multiple sites within right and

Table III

		Atrium			AV node		
		CL	*FRP*	*ERP*	*RRP*	*FRP*	*ERP*
Case 1	C	700	260	260	360	325	260
	D	700	250	250	360	315	260
Case 2	C	900	320	285	740	395	320
		700	300	230	625	380	≶300
	D	900	330	250	800	415	≶330
		700	310	230	650	390	310
Case 3	C	900	320	280	720	≶360	≶320
		800	280	240	480	≶330	≶280
		700	290	270	585	≶335	≶290
		600	270	250	360	325	≶270
	D	800	270	250	540	330	≶270
Case 4	C	1100	280	240	725	415	≶280
		550	≶380*	≶380*	≷540	445	390

All measurements are in msec
CL = cycle length C = control D = after IV strophanthin
FRP = functional refractory period ERP = effective refractory period
*Shorter atrial coupling intervals were not attempted

control state ranged from 320 to 260 msec, tended to be shortened by reduction in paced atrial cycle length, and was the rate limiting determinant of AV conduction only in Case 3 It was not significantly altered by strophanthin The *AV nodal functional refractory period* in the control state, varied from 325 to 445 msec in the three patients in whom it could be determined and its response to alteration in paced cycle length was variable As the paced atrial cycle length was decreased the FRP (AVN) increased in one patient, and decreased in the other two The AV nodal FRP was the rate limiting determinant of conduction in three of the four cases The *AV nodal effective refractory period* (ERP) could then only be determined in three patients and ranged from 260 to 390 msec It was not significantly altered by strophanthin and was also variably affected by reduction of the paced atrial cycle length Refractoriness of the His Purkinje system was not a rate limiting determinant of AV conduction in any case

The *relative refractory period of the AV node* in the control state was short only in Case 1 (RRP = 360 msec at CL = 700 msec) Following strophanthin the RRP remained unchanged in Case 1, but was lengthened in the other two cases Neither reciprocating tachycardias nor changes in QRS morphology suggesting ventricular pre excitation were observed during extrastimulus studies either before or after strophanthin No attempt was made by ventricular premature stimulation to exclude the presence of a concealed accessory pathway with only retrograde V A conduction

Discussion

Although over 60 cases of atrial flutter with 1:1 AV conduction have been reported previously[3] in many of these cases the electrocardiographic diagnosis has been open to dispute particularly when the QRS complexes have been wide the rates less than 230/minute and atrial flutter with higher grades of AV block has not been demonstrated For this reason we have used relatively rigid criteria for the diagnosis of atrial flutter with 1:1 AV conduction and although the selection of a rate of 230/minute or more is an arbitrary one it is supported by previously reported studies of atrial flutter[13] and also emphasizes the phenomenon of 1:1 AV conduction at rapid atrial rates, irrespective of the type of supraventricular arrhythmia

Very few electrophysiological studies of patients with atrial flutter and 1:1 AV conduction have been reported Durrer[7] described a 38 year old woman with a short PR interval (07 sec) who presented with attacks of supraventricular tachycardia with 1:1 AV conduction (rate 250/minute) in whom catheter manipulation in the right atrium during electrophysiological study resulted in a similar tachycardia requiring electrical cardioversion Her AV conduction time during right atrial pacing was only 70 msec suggesting an AV nodal bypass Wellens investigated a 35 year old woman with a PR interval of 12 sec who had an 18 year history of palpitations due to supraventricular tachycardia at a rate of 220/minute He found evidence of a probable anomalous AV connection from left atrium to an area close to the tail of the AV junction During this study atrial overdriving of the supraventricular tachycardia at 300/minute provoked atrial flutter with 1:1 AV conduction (rate 270/minute) with rapid loss of consciousness A more detailed investigation in a 43 year old man with documented atrial flutter and 1:1 AV conduction (rate 270/minute) has been reported by Aranda and colleagues[5] In this patient the PR interval was 16 sec and the maximal pacing rate was 215/minute with an AH increment (ΔAH) of 35 msec and an AH gradient of 25 The onset of the AV nodal RRP was shortened at 335 msec the AV nodal FRP was 350 msec, and the AV nodal ERP was less than 280 msec All refractory periods

Leukocyte ıntracellular catıons ın hypertensıon
Effect of antıhypertensıve drugs

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Ibrahım M Khatrı M D
Lında L. Yao M S
Edward D Freıs M D
Washıngton D C

There ıs a consıderable body of evıdence which ındıcates that sodıum (Na) ıs an ımportant factor ın the development of hypertensıon Epıdemıologıc studıes have shown that unaccul turated peoples who have no access to salt do not develop hypertensıon ın contrast to all salt eatıng socıetıes where hypertensıon ıs common Clınıcal studıes have documented that reductıon ın body sodıum usıng saluretıc agents or low salt dıets often lowers blood pressure[3] Experımental studıes have shown that hypertensıon can be ınduced ın susceptıble straıns of rats by salt loadıng Most studıes to date have been concerned with the assessment of total extracel lular and plasma volumes and of extracellular Na concentratıon as methodologıcal problems have made ıt dıffıcult to measure the ıntracellular content of Na ın man However methods have been developed recently for determınıng Na and other catıons ın leukocytes These represent lıvıng nucleated cells that are easıly obtaıned by venıpuncture Recently Edmonson and asso cıates[4] reported that the Na and water content of leukocytes (WBC) ıs ıncreased ın hypertensıve patıents In the present study the WBC Na potassıum (K) magnesıum (Mg) and water content have been determıned ın normal subjects and ın patıents wıth essentıal hypertensıon

No ınformatıon ıs presently avaılable regardıng the effect of antıhypertensıve drugs on ıntracellu lar catıons Therefore we have also determıned ıntracellular water and catıon changes ın leuko cytes (WBC) before and after treatment wıth four antıhypertensıve agents hydrochlorothıazıde (HCTZ) reserpıne (RES) alpha methyldopa (AMD) and hydralazıne (HDZ)

Materıals and methods

Comparıson of normotensıve and hypertensıve subjects The study group comprısed 32 normo tensıve men and 47 male patıents wıth uncomplı cated hypertensıon The blood pressure of the hypertensıve patıents taken ın the sıttıng posıtıon ranged between 130/96 and 190/128 mm Hg wıth an average mean blood pressure (MBP) of 126 mm Hg MBP was estımated by takıng the sum of the dıastolıc blood pressure and one thırd of the pulse pressure The blood pressure of the normal subjects ranged between 100/70 and 160/ 86 mm Hg wıth an average MBP of 95 mm Hg The average age of the hypertensıve patıents was 47 years as compared to 44 years ın the normal group No patıents wıth renal or cardıac faılure were ıncluded the hıghest serum creatının level beıng 2 2 mg per cent Forty fıve patıents had not receıved prevıous antıhypertensıve drug therapy whıle ın the remaınder treatment had been dıscontınued for 4 weeks or longer prıor to draw ıng the blood samples

Effects of antıhypertensıve agents The study group comprısed 51 hypertensıve patıents The followıng crıterıa were used for selectıng these subjects eıther no prıor treatment or absence of any antıhypertensıve drug medıcatıon wıthın a perıod of at least four weeks prıor to the study dıastolıc blood pressure of 90 to 114 mm Hg

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Receıved for publı tıon J n 20 19 8
Accepted f r publıcat on M y 12, 1978

Reprınt requests Edward D Freıs, M D V A Hosp tal, 50 Irvıng St N W Washıngton D C 20422.

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left atria and coronary sinus, these suggested mechanisms must remain speculative

Summary

Electrophysiological studies of atrioventricular conduction during rapid atrial overdrive pacing and during programmed premature atrial stimulation are reported in four patients with an unusually rapid 1 1 ventricular response to atrial flutter (ventricular rates 240 to 310 per minute) Second degree AV block developed during atrial overdrive pacing at rates well below those during which 1 1 AV conduction was sustained during spontaneous atrial flutter Although none of the four patients showed evidence of pre excitation on the standard 12 lead electrocardiogram, evidence suggesting a partial AV nodal bypass was demonstrated at electrophysiological study in one case It is postulated that the profile of the atrial wavefront presented to the normal AV node by atrial flutter differs from that during high right atrial pacing and may account for the lower ventricular rates achieved during high right atrial overdrive pacing than during spontaneous atrial flutter in the remaining three cases

The authors express their appreciation to the Medical Superintendent of Groote Schuur Hospital for permission to publish these findings to Miss Alison Shennan and Mr L W Piller for technical help and to Miss M Kavalsky for secretarial help

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Table III Comparison of hypertensive patients (P) with normal controls (N) by age groups

Age (yrs)	Subjects Type	Subjects No	Mean blood pressure Average mm Hg	Mean blood pressure Comparison of N with H	WBC Na content Average mEq / Kg wcw	WBC Na content Comparison of N with H
<30	N	5	89 0		?0 7	
	H	3	11?0	P < 0025	26 7	P < 01
30-39	N	4	89 9		15 8	
	H	6	126 2	P < 0005	?8 5	P < 05
40-49	N	9	100 9		21 1	
	H	17	128 8	P < 0005	28 1	P < 05
50-59	N	8	94 8		20 7	
	H	19	1?5.2	P < 0005	?2 8	NS
>60	N	3	9/0		20 0	
	H	2	134 5	P < 00?5	17 4	NS

wcw = w t cell w ght

The reproducibility of the measurement was checked by repeating the determinations one week to 3 months apart in 10 normotensive control subjects and in 16 patients with hypertension All samples were code numbered so that the biochemist was blinded as to the identity of the samples

Results

Comparison of normotensive and hypertensive subjects The results are illustrated in Tables I to III Table I shows the reproducibility of the WBC cation determination In the 10 controls (N) and in 16 patients (H) who had two blood samples one week to three months apart there were no statistically significant differences between the values in the first determination as compared to those of the second The r values correlating the two determinations were statistically significant (P < 005 for Na P < 0005 for K and P < 0005 for Mg)

Table II indicates that the WBC Na content was significantly higher in hypertensive patients (average 25 5 mEq /Kg wet cell weight (wcw) than in the control group (average 19 7 mEq /Kg wcw [(P < 01]) The percentage distribution of WBC sodium values are plotted in Fig 1 The percentage of hypertensive patients at the low end of the scale of sodium concentrations is small whereas there is a preponderance of such patients at the high end The curve for the hypertensive patients appears shifted to the right although in the mid range of sodium values the percentage

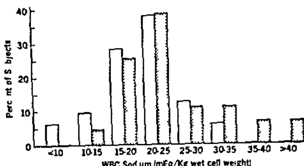


Fig 1 Percentage distribution of the sodium concentration of leukocytes in normal subjects *(clear columns)* and hypertensive patients *(black columns)* The distribution for the hypertensive subjects appears shifted to the right

distribution is essentially the same in both groups Differences in WBC K and Mg or water content and in serum Na and K as well as in body weight were not significant in patients as compared to the normal subjects

Table III indicates the differences in WBC Na between normal and hypertensive subjects according to age group It shows that whereas the MBP was significantly increased in hypertensive patients as compared to the controls of the same age in all age groups (P < 0025 to P < 0005) the WBC Na content was higher in hypertensive patients as compared to controls only in the age groups under 50 years (P < 05 to P < 01) and not in the older patients

Effects of antihypertensive agents All drug regimens resulted in a significant reduction in MBP after 48 hours two weeks and four weeks (Table IV) Whereas the average fall in MBP was somewhat greater with HCTZ than with the other drugs (Table VI) statistically there was no significant difference between the various regimens

WBC Na fell significantly in the patients who received HCTZ or RES (Table V) The reduction in extracellular Na was evident at 48 hours after either drug and decreased further over the subsequent 4 weeks Neither HDZ nor AMD however produced any significant change in WBC Na While the mean reduction in WBC Na associated with HCTZ was greater than with RES the difference between the two was not significant

The initial mean values of WBC Na were lower in the groups receiving HDZ or AMD than in those receiving HCTZ or RES Since this might have influenced the results the data were further analyzed in each drug group according to whether

Table I Reproducibility of WBC cation determinations

Variable	Mean of first determination	Mean of second determination	Significance of difference	r*
Normal controls (10)				
Na mEq/Kg wcw	16.7	18.5	NS	.87‡
K mEq/Kg wcw	116.2	113.7	NS	.97‡
Mg mEq/Kg wcw	19.0	19.2	NS	.81‡
H_2O % wcw	64.6	65.0	NS	.84‡
Hypertensive patients (16)				
Na mEq/Kg wcw	25.0	24.2	NS	.64‡
K mEq/Kg wcw	116.7	115.1	NS	.91‡
Mg mEq/Kg wcw	19.9	19.5	NS	.84‡
H_2O % wcw	64.3	65.8	NS	.50†

*The correlation coefficient measuring the relationship between the first and second determinations
wcw = wet cell weight
‡P < .005
†P < .0[illegible]5

Table II Comparison of 47 hypertensive patients (H) with 32 normal control subjects (N)

Variable	Subjects: Type	Subjects: No	Mean and standard deviation	Comparison of N and H
Age (yrs)	N	32	44.0 ± 12.3	NS
	H	47	46.9 ± 8.9	
Body weight (lb)	N	27	177.2 ± 28.8	NS
	H	47	183.3 ± 4[illegible].4	
MBP (mm Hg)	N	32	94.7 ± 8.8	P < .001
	H	47	126.1 ± 11.3	
WBC Na (mEq/Kg wcw)*	N	32	19.7 ± 6.2	P < .01
	H	47	25.5 ± 7.7	
WBC K (mEq/Kg wcw)	N	32	113.1 ± 11.9	NS
	H	47	118.0 ± 11.5	
WBC Mg (mEq/Kg wcw)	N	32	19.8 ± 1.6	NS
	H	47	19.8 ± 2.3	
H_2O % wcw	N	32	63.2 ± 8.8	NS
	H	47	64.5 ± 3.4	
Serum Na (mEq/L)	N	31	141.7 ± 3.5	NS
	H	47	143.1 ± 3.7	
Serum K (mEq/L)	N	31	4.2 ± 0.5	NS
	H	47	4.3 ± 0.5	

wcw = wet cell weight.

inclusive on two or more consecutive visits or 115 to 124 mm Hg on the initial visit. Patients with diastolic blood pressure of 115 mm Hg or higher at the initial visit were begun on treatment without a second visit.

The patients were randomly assigned to one of the following drug regimens given orally: 14 patients received HCTZ 50 mg twice daily; 13 patients were given RES 0.25 mg 3 times daily for 2 days and then 0.25 mg daily, 13 received AMD 250 mg 3 times while 13 patients were given HDZ 25 mg 3 times daily. If the initial dose of HDZ or AMD failed to reduce the diastolic pressure by 5 mm Hg or more below the pretreatment level and to below 90 mm Hg diastolic, the dose was increased on succeeding visits to maximum doses of 150 mg per day HDZ and 1,500 mg per day AMD.

Before initiating treatment two control blood samples for WBC and serum electrolytes were drawn one week apart, except for patients with diastolic blood pressure of 115 mm Hg or higher who had only one control blood sample. Further blood samples were drawn at 48 hours, at 2 weeks and finally at 4 weeks after beginning drug administration.

Blood pressure and pulse rate in the sitting position, body weight, and incidence of side effects were recorded at each visit. Mean blood pressure (MBP) was estimated by the sum of the diastolic blood pressure plus one third of the pulse pressure.

The method of Baron and Ahmed[5] for measuring WBC cations and water content was used with modifications introduced by Edmondson and associates[6] and by ourselves. A summary of the method is as follows: blood was drawn from an antecubital vein with minimal suction to avoid frothing and transferred in 8 c.c. aliquots into graduated tubes containing Dextran and heparin. The blood was allowed to sediment for 30 minutes and the WBC layer pipetted off. After centrifugation the sediment was diluted and the residual red blood cells were lysed. After a second centrifugation the WBC were transferred to a platinum crucible, weighed, dried and weighed again. They were then ashed and the cations were measured by atomic absorption spectrophotometry. The extracellular fluid volume trapped within the leukocyte mass was determined by adding I[131] labelled human serum albumin and measuring its volume dilution. All samples were measured in duplicate.

Table V Changes in WBC cations and per cent water content during treatment

Drug	Time	Number of patients	WBC Na (mEq / Kg)¶	Change	WBC K (mEq / Kg)¶	Change	WBC Mg (mEq / Kg)¶	Change	Percent water content	Change
HCTZ	Control	14	25 7 ± 12 7	–	1?4 ± 19 7	–	?0 1 ± 2 9	–	64 9 ± 3 0	–
	48 Hours	13	19 4 + 10 0	–7 6‡	123 ± 17 0	–0.5	20 1 ± 2 7	0	64 4 ± 4 9	0
	? weeks	12	14 9 ± 4 2	–8 7§	1?4 ± 10 2	–0 1	20 0 ± 1 8	0	6? , ± 5 1	–2 9†
	4 weeks	11	14 8 ± 4 3	–11 0‡	1 2 ± 10 6	–1.2	19 9 ± 1 4	–0 2	63 0 ± 3 1	–2 0
HDZ	Control	11	19 6 ± 5 7	–	118 ± 5 8	–	19.2 ± 1 9	–	63 6 ± 2 7	–
	48 Hours	11	17 7 ± 6 5	–1 8	119 ± 7 ?	0	19 3 + 1 7	0	62 5 ± 4 5	0
	2 Weeks	10	20 7 + 6 5	+0 9	115 ± 4 6	–2 8	18 8 ± 1 4	0	64 9 ± 2.2	0
	4 Weeks	9	20 1 + 8 6	–0 1	115 ± 7 0	–1 9	19 2 + 2 2	0	63 9 ± 4 9	0
RES	Control	13	26 3 ± 10 8	–	120 ± 4 8	–	20 7 ± 2 4	–	65 1 ± 2.3	–
	48 Hours	13	18 4 ± 6 5	–7.9†	115 ± 12 0	–2 4	20 2 ± 1.3	–0.2	65 2 ± 3.5	0
	2 Weeks	13	16 5 ± 6 3	–9 9‡	119 ± 5 5	0	19 7 ± 1.2	–0 5	66 1 ± 2.2	+1 0
	4 Weeks	11	20 0 ± 9 1	–7 9†	117 ± 6 6	–1 2	19.2 ± 1.2	–0 6	67 1 ± ? 1	+2.3†
AMD	Control	13	20 7 + 6 7	–	116 ± 6.0	–	19 ? ± 1 7	–	64 9 ± 2 9	–
	48 Hours	13	19 7 + 6 6	–1 0	116 ± 7.3	0	19 ? ± 2 1	0	65 0 ± 2 7	0
	2 Weeks	13	17 3 + 6 5	–4.2†	118 ± 4 9	+1.3	19 6 ± 1.3	0	65.2 ± 2 4	0
	4 Weeks	12	19 4 ± 8 2	–0 8	116 ± 5.5	0	19 2 ± 1.5	0	65 5 ± 3 4	+0 4

See Table I
†P < 05
‡P < 01
§P < 001
¶ mEq /Kg w t cell weight.

Na /Kg wcw and 63 2 per cent cell water respectively These authors found a somewhat higher concentration of cell potassium averaging 137 mEq /Kg wcw as compared to our mean of 114 mEq /Kg wcw

Interest in the Na and water content of cells in hypertensive patients stems from the observation of Tobian and Binion[7] who in 1952 reported increased amounts of both in the renal arteries of hypertensive patients The determination of intracellular cations in hypertension using cardiac or skeletal muscle brain and erythrocytes have resulted in inconclusive and conflicting results[7,8] Part of the difficulty might be due to the lack of reliable methods for measuring the extracellular space in complex tissues Since the extracellular concentration of Na is far higher than the intracellular content only small errors in estimating the extracellular space surrounding the cells can lead to considerable deviations from the true intracellular Na content This problem is not present with the erythrocyte but because of its unique structure and function it may not be representative of other living cells However WBC are nucleated cells and also are not bound to other cells so that the fluid trapped between the packed WBC can be accurately measured by mixing with an extracellular indicator

The present results confirm the observations of Edmondson and associates[6] that the Na content of WBC is increased in patients with essential hypertension Edmondson and colleagues found a mean increase of 29 per cent in WBC Na of hypertensive patients which is the same as was determined in the present study Our data however indicated that the increase is found primarily in hypertensive patients below the age of 50 whereas Edmondson and associates did not observe any age differences Edmondson and colleagues studied fewer patients and it is possible that their series was too small to detect differences in subgroups

The significance of the increased WBC Na in hypertension requires further clarification Evidence for an intracellular shift of Na associated with a rise of blood pressure had been presented by Friedman and co workers They observed that pressor doses of pitressin norepinephrine and angiotensin intravenously resulted in a shift of Na with variable amounts of water from the extracellular fluid into the cells A reverse shift occurred as the pressor reaction wore off Friedman and colleagues believed that the Na shift preceded the rise of blood pressure and was in fact instrumental in bringing about the vasoconstrictor response However there is no certain

Table IV Mean blood pressure, body weight and serum Na and K changes during treatment

Drug	Time	Number of patients	Mean blood pressure (mm Hg)	Change**	Body weight (lb)	Change**	Serum Na (mEq /L)	Change**	Serum K (mEq /L)	Change
HCTZ	Control	14	128 ± 12	–	183 ± 52	–	144 ± 3.9	–	4.2 ± 0.5	–
	48 Hours	13	116 ± 8	−11 6§	183 ± 52	0	141 ± 4 4	−3 1†	4 0 ± 0 5	−0 ?
	2 Weeks	12	109 ± 11	−18 6‡	178 ± 51	−2 5†	143 ± 3 8	−1 0	4 0 ± 0 4	−0.2
	4 Weeks	11	105 ± 12	−22 2‡	177 ± 54	−1 8	143 ± 2 7	−1 1	3 9 ± 0 4	−0 34†
HDZ	Control	11	129 ± 13	–	194 ± 38	–	140 ± 3 4	–	4 0 ± 0 5	–
	48 Hours	11	120 ± 12	−8 6§	194 ± 38	0	142 ± 4 0	+1 0	4 0 ± 0 7	0
	2 Weeks	10	120 ± 13	−10 6‡	199 ± 35	+1 2	141 ± 3 3	+0 6	4 1 ± 0 6	+0 04
	4 Weeks	9	112 ± 15	−17 9‡	198 ± 38	+0 8	141 ± 3 3	+0 4	4 0 ± 0 6	0
RES	Control	13	122 ± 10	–	198 ± 42	–	143 ± 2 8	–	4 4 ± 0 6	–
	48 Hours	13	110 ± 14	−11 4§	199 ± 41	0	144 ± 3 3	+0 6	4 2 ± 0 4	−0 ?5
	2 Weeks	13	112 ± 7	−9 9‡	199 ± 41	0	145 ± 3 8	+1 8	4 1 ± 0 5	−0 3
	4 Weeks	11	110 ± 8	−13 2§	196 ± 42	−0 5	145 ± 3 4	+2 9†	4 3 ± 0 5	−0 16
AMD	Control	13	124 ± 10	–	178 ± 45	–	145 ± 3 7	–	4 1 ± 0 3	–
	48 Hours	13	113 ± 9	−10 9§	178 ± 44	0	143 ± 2 9	−2 1†	3 8 ± 0 6	−0.24
	2 Weeks	13	109 ± 24	−15 1‡	177 ± 45	0	144 ± 3 0	−1 0	4 2 ± 0 5	+0 5
	4 Weeks	12	114 ± 17	−10 6‡	177 ± 46	0	145 ± 5 5	0	4 3 ± 0 4	+0 18

HCTZ = hydrochlorothiazide 50 mg twice daily HDZ = hydralazine 25 mg 3 times daily RES = reserpine 0 75 mg daily for 2 days and then 0.25 mg daily AMD = alpha methyldopa 250 mg 3 times daily

When there were fewer patients at a follow up interval than were present in the control period the difference was calculated from the mean control value of the patients remaining in the study at the particular interval

†P < 05
‡P < 01
§P < 001

the initial level of WBC Na was low or high The median pretreatment value for all of the patients of 21 8 mEq /Kg wcw was used as the dividing line between low and high subgroups The results shown in Table VII indicate a marked difference between low and high subgroups in the patient taking HCTZ However, there was no difference in the degree of reduction seen in the low and high subgroups who were given RES Changes were small in both low and high subgroups receiving HDZ or AMD and remained insignificant even when the two groups were combined

HCTZ also resulted in 2 9 per cent (P < 05) reduction in the cell water content after two weeks and a 2 0 per cent reduction (P > 05) after four weeks Percentage of cell water increased slightly after reserpine, becoming significant (P < 05) at the fourth week of treatment No change was observed in cell water content until 2 weeks after RES Cell water content remained essentially unchanged after HDZ and AMD None of the drugs included HCTZ was associated with significant changes in either WBC K or Mg (Table V)

As expected serum K decreased during treatment with HCTZ although the change was small reaching the level of significance (P < 05) at the fourth week after beginning the drug Serum Na showed little change after any of the drugs but occasionally the change reached the level of significance (P < 05) Such a decrease occurred at 48 hours after HCTZ and AMD but was not maintained and an increase occurred at the fourth week after RES However, sporadic fluctuation of this type occurring in small sample sizes probably are due to chance variation There was a mean loss of six pounds body weight after HCTZ and a mean gain of four pounds following HDZ Body weight did not change appreciably after RES or AMD

Discussion

The reproducibility of the measurements of WBC cations and water content was tested by repeating the measurements one to 12 weeks apart The correlation coefficients indicated good agreement between the two measurements in each subject despite a wide range of values between subjects The actual values for WBC sodium and water content in normal subjects agreed closely with those previously published by Baron and Ahmed [3] who reported mean values of 22 2 mEq Na /Kg wcw, and 64 1 per cent cell water as compared to our values of 19 7 mEq

Table V Changes in WBC cations and per cent water content during treatment

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	2 weeks	12	14 9 ± 4 2	−8 7§	124 ± 10 2	−0 1	20 0 ± 1 8	0	62 5 ± 5 1	−2.9†
	4 weeks	11	14 8 ± 4 3	−11 0‡	122 ± 10 6	−1 2	19 9 ± 1 4	−0 2	63 0 ± 3 1	−2 0
HDZ	Control	11	19 6 ± 5 7	—	118 ± 5 8	—	19 2 ± 1 9	—	63 6 ± 2 7	—
	48 Hours	11	17 7 ± 6 5	−1 8	119 ± 7 2	0	19 3 ± 1 7	0	62.5 ± 4 5	0
	2 Weeks	10	20 7 ± 6 5	+0 9	115 ± 4 6	−2 8	18 8 ± 1 4	0	64 9 ± 2 2	0
	4 Weeks	9	20 1 ± 8 6	−0 1	115 ± 7 0	−1 9	19 2 ± 2.2	0	63 9 ± 4 9	0
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	48 Hours	13	19 7 ± 6 6	−1 0	116 ± 7 3	0	19 2 ± 2 1	0	65 0 ± 2 7	0
	2 Weeks	13	17 3 ± 6 5	−4 2†	118 ± 4 9	+1 3	19 6 ± 1 3	0	65.2 ± 2 4	0
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See Table I
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¶ mEq /Kg. wet cell weight

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Table VI Comparison between mean* changes for the 4 weeks following HCTZ and the other antihypertensive agents

Drug regimen	*Mean blood pressure (mm Hg)*	*WBC Na (mEq /Kg)†*	*WBC water (% wet cell weight)*
HCTZ	−17 00	−9 29	−2 00
HDZ	−11 18	−0 58	+0 00
Significance	NS	‡	NS
HCTZ	−17 00	−9 29	−2 00
RES	−11 31	−8 35	+2 27
Significance	NS	NS	NS
HCTZ	−17 00	−9 29	−2 00
AMD	−11 38	−2 38	+0 50
Significance	NS	§	NS

NS = not statistically significant
Mean changes represent the average of all three determinations taken during the treatment period as compared to the pretreatment control period
†mEq /Kg wet cell weight
‡P < 001
§P < 05

Table VII Influence of low and high initial WBC Na content on response to antihypertensive agents

Drug	*Low initial WBC Na†*			*High initial WBC Na†*		
	No pts	*Mean change mEq / Kg wcw*	*P value†*	*No pts*	*mEq / Kg wcw*	*P value*
HCTZ	6	−2 7	NS	7	−18 3	< 01
HDZ	7	+2 2	NS	3	−3 3	NS
AMD	7	−0 7	NS	6	−1 0	NS
RES	4	−8 0	< 05	9	−8 0	05
HDZ+ AMD	14	+0 7	NS	9	−3 7	NS

The division between low and high WBC Na was done by taking the median value in the pretreatment period using the data from all patients This value was 21 8 mEq Na /kg wet cell weight of WBC
†Change from pretreatment

evidence that the Na shift they observed was the cause or the effect of the pressor response, nor is it possible to relate directly the changes observed in patients with chronic hypertension to the results of acute elevation of blood pressure in animals induced by pressor hormones

The role of Na in vascular smooth muscle contraction and its possible relationship to hypertension has recently been reviewed by Haddy and Overbeck[10] and by Blaustein[11] The ratio (Na) / (Na) is important in regulating the amount of intracellular calcium An increase in calcium ions within the cell triggers smooth muscle contraction, and smooth muscle tension is dependent on the concentration of intracellular calcium A decrease in the (Na) /(Na)$_i$ by either a decrease in (Na) or an increase in (Na)$_i$ will result in a movement of calcium into cells The above authors postulate that in hypertension total peripheral resistance is increased because of an increase of Na in vascular smooth muscle cells The increase could occur either through passive leakage of Na into the cells or a failure of the intracellular sodium pump They suggest that a circulating hormone possibly the natriuretic hormone,' controls this change in the Na gradient While admittedly speculative it is of interest that the present findings support this hypothesis at least with respect to the WBC

No significant differences were observed in the WBC content of K and Mg in the hypertensive patients as compared to the normal subjects Also in contrast to Edmondson and co workers* who found an increased WBC water as well as Na content in hypertensive patients, we found no difference in the percentage of cell water between hypertensive and normal subjects The reason for this discrepancy is not apparent Similar methods were used in both studies

While the observation of an increase in WBC Na in hypertension is of considerable interest and possible importance it should be emphasized that other body cells may not share in this change and that the observed cation abnormality in hypertensive patients may be peculiar to WBC and not to other cells Furthermore, the distribution of WBC sodium levels in hypertensive patients may signify the presence of two populations a larger group with normal values and a smaller group with elevated levels Except for the preponderance of patients under age 50 we were unable to identify any other distinguishing features that would characterize the latter group Further investigation is needed to clarify the pathogenic significance of these findings

With respect to the changes observed after the various antihypertensive agents, it should be noted that all were effective in significantly reducing MBP In addition to lowering the MBP, HCTZ resulted in a significant reduction in WBC Na Both blood pressure and WBC Na were significantly reduced as early as 48 hours after

administration of HCTZ and both were maintained throughout the four weeks of study There also was a loss of WBC water after HCTZ This reduction was not present until after the first 48 hours of treatment and was of relatively small magnitude in comparison with the loss of WBC Na

The serum Na concentration remained constant after HCTZ throughout the period of the study This observation is consistent with prior studies indicating that the drug produces a loss of extracellular water and Na in isotonic proportion The result of the reduction in intracellular (WBC) Na concentration and unchanged extracellular Na concentration was a rise in the WBC extra/intracellular Na (Na /Na ,) gradient A similar relationship between intracellular Na and MBP changes was described by Friedman and colleagues [13] who found in animals an increase in the Na /Na gradient associated with an acute fall in blood pressure

The literature concerning the effects of the thiazide diuretics on the intracellular cations and water is conflicting Muscle biopsies have been taken in man before and after treatment with HCTZ by two groups of investigators who report almost diametrically opposite results Vilamil and associates found a decrease in both intracellular sodium and water following 3 to 7 weeks of treatment with HCTZ in hypertensive patients These observations are therefore similar to the present findings in WBC On the other hand Bergstrom and Hultman found after one week of treatment with HCTZ in normal subjects a significant increase in the intracellular Na concentration of muscle Still a third result was obtained in vascular smooth muscle of rats by Tobian and associates They found the Na and water content of small artery smooth muscle to remain unchanged following chlorothiazide

Other types of studies suggest that the principal effect of the thiazide diuretics is on the extracellular fluid volume rather than on the water and electrolyte content of the cells Several investigators have found that treatment with chlorothiazide or HCTZ is associated with decreased extracellular and plasma volumes [?] Freis observed that during the first 4 or 5 days following the administration of chlorothiazide all of the excess loss of Na and water in the urine could be accounted for by the decrease in extracellular fluid volume The present results indicate that the major loss of WBC Na occurred within the first 48 hours although there was a further small progressive loss following that interval While there is no ready explanation for the present findings it is possible that because of their location in the circulation WBC are unusually responsive to changes in extracellular and plasma volume a characteristic that is not shared by other body cells

The hemodynamic response within the first week of treatment with thiazides is a reduction in cardiac output and an increase in total peripheral resistance [20,2] This latter finding would appear to be inconsistent with Friedman and colleagues theory of a primary Na shift in vascular smooth muscle producing a decrease in total peripheral resistance Against the Friedman and associates hypothesis also is the fact that the reduction of blood pressure associated with HDZ or AMD was not accompanied by any significant change in WBC Na Again such changes could occur in vascular smooth muscle and not in WBC

It is puzzling that the administration of RES was associated with a significant reduction in WBC Na This change was present after 48 hours and was maintained throughout the study At present it is not clear whether the observed changes in WBC Na were related to the antihypertensive actions of HCTZ and RES or were independent effects An increase in percentage of cell water was recorded after RES However the change was quite small barely reaching the level of significance and only at the fourth week of treatment The increase therefore could have occurred by chance rather than being drug related

None of the four drugs used in this study was associated with significant changes in WBC K or Mg (Table V) although HCTZ resulted in the well known fall in serum K However it is doubtful that the hypokalemia reflects a similar change in total body K The most recent studies using the total body counter failed to disclose a significant decrease in total body K during prolonged treatment of hypertensive patients with oral diuretics [22, 3] Maronde and co workers [4] collected urine and stool samples on a metabolic ward in hypertensive patients The cumulative loss of K over 7 days of thiazide treatment indicated negligible reduction in total body stores In all of the above studies there was a significant reduction in serum K concentration which obviously did not reflect an intracellular deficit The present results are consistent with

other evidence that the reduction in serum concentration of K^+ is not a reflection of a major intracellular loss

Summary

Leukocyte (WBC) cations were determined in 32 normotensive control subjects and in 47 age matched patients with uncomplicated hyperten sion The intracellular concentration of sodium (Na) which averaged 25 5 mEq /Kg wet cell weight (wcw) in the hypertensive patients was significantly higher (P < 01) than in the control subjects (average 19 7 mEq /Kg wcw) Elevated WBC Na was observed only in the hypertensive patients under age 50 years WBC potassium, magnesium and percentage water content were not significantly different in hypertensive pa tients as compared to the control subjects The finding of an increased intracellular Na content in hypertensive patients is consistent with recent observations relating the extracellular/intracel lular Na gradient to vascular smooth muscle tension and to the control of the peripheral vascular resistance

WBC cations also were determined after treat ment with hydrochlorothiazide, hydralazine, re serpine or alpha methyldopa Hydrochlorothia zide was associated with a reduction in WBC sodium content (P < 01) Reserpine also was associated with a lesser fall in WBC sodium (P < 05) Cell water content decreased slightly after hydrochlorothiazide (P < 05), but in creased slightly following reserpine (P < 05) Changes in WBC, sodium or water were not significant following alpha methyldopa or hydral azine None of the drugs were associated with changes in WBC potassium or magnesium, although serum potassium concentration de creased significantly (P < 05) with hydrochloro thiazide

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Significance of P wave terminal force in presumably healthy middle aged men

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The finding of an abnormal P terminal force in Lead V_1 (V Ptf) a concept introduced by Morris and associates[1] in 1964 has been demonstrated in both acute and chronic left sided heart diseases[2-4] In most of these studies a significant correlation has been found between left ventricular filling pressure and the magnitude of V Ptf *Recently* V_1*Ptf* was shown to correlate significantly with left atrial dimensions as measured by echocardiography in various cardiac diseases and Josephson and associates[2] have suggested that an interatrial conduction defect may be the underlying cause for abnormal V Ptf

The discriminative performance of V Ptf in coronary heart disease (CHD) versus normals seems to be questionable[5-9] Most previous studies on V_1Ptf have been performed in patients with proven heart disease Increased V_1Ptf is however occasionally seen in routine electrocardiograms of apparently healthy individuals and the significance of this finding in relation to latent cardiac disease is not yet defined The aims of the present study were (1) to assess the prevalence of abnormal V Ptf in presumably healthy males and (2) to evaluate the significance of this finding in relation to latent CHD and various physiological parameters

Material and methods

The present study comprises 695 males with mean age 49 5 years range 40 to 60 years selected among the first 1 000 of 2 014 males who participated in an epidemiological study on latent CHD[13] They were all working at five preselected firms or state agencies in Oslo Norway Prior to the survey a careful selection of men thought to be healthy was performed by excluding all with known CHD other heart disease hypertension under treatment, diabetes mellitus malignancy disorders of the locomotive system preventing a near maximal bicycle exercise test and miscellaneous disorders (advanced *pulmonary disease* renal disease liver disease etc) The examination included a comprehensive case history complete physical examination *laboratory tests* chest x ray with measurement of heart volume[1] phonocardiogram resting electrocardiogram (ECG) exercise ECG during a near maximal bicycle exercise test and postexercise ECG This examination program revealed a considerable number of cases with findings suggesting heart disease In the men in whom the survey examination suggested the presence of CHD coronary angiography was performed as described elsewhere[13] For an angiogram to be called positive an obstruction of a major coronary artery $\geq$ 50 per cent had to be present and among the positives all except 5 had at least one obstruction of 75 per cent or more The diastolic blood pressures used were measured at phase 4

Either of the following findings revealed during the examination program was a cause for exclusion from the main study (a) systolic murmur of grade 3 or *more* (*b*) diastolic murmur (c) heart volume 500 ml /M or more (d) ECG patterns of myocardial infarction (e) left ventricular hypertrophy (f) left or (g) right bundle branch block (Minnesota Codes 1 1 3 1 7 1 and 7 3 respective

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Received for publ tio J 26 1978
Accepted f publ ti n M y 5 1978

Reprint requests D Kolbjorn Forfa g Med. a d B Rikshosp talet Oslo 1 N rw y

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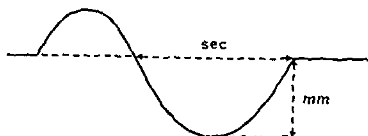


Fig 1 Measurements for calculation of V Ptf

ly[1] (h) a positive WHO questionnaire on angina pectoris[11] and (i) a positive exercise ECG

To assess the possible difference in V_1Ptf between normals and individuals with latent CHD, 95 of the 105 angiographied males were selected, representing all with a strong suspicion of CHD and none of the exclusion criteria (a) through (g) (*see above*)

The study on interobserver variation in the measurements of V_1Ptf was performed on ECG's from both groups All ECG s were read separately and blindly by both authors

ECG s were recorded with a direct writing ink jet Mingograf (Elema Schonander) with a paper speed of 50 mm per second The estimations of V_1Ptf were performed according to the method of Morris and associates[2] Measurements of amplitude were made down to the nearest 0 25 mm, and duration down to the nearest 0 1 second The terminal force is defined as the product of the amplitude in millimeters (1 mm ≈ 0 1 mV) and the duration in second of a possible negative terminal portion of the P wave (Fig 1) Abnormal V_1Ptf values is defined as ≤ – 0 03 mm second The measurements of V_1Ptf were made separately on the resting ECG s and on the ECG s recorded five minutes after the near maximal exercise test[13] Except for the results on interobserver variation the measurements used refer to the readings made by one of us (K F)

The statistical evaluations were made by linear correlation analyses one and two way analyses of variance and multiple t tests

Results

Abnormal V_1Ptf (≤ – 0 03 mm second) at rest was found in 49 of the 695 presumably healthy males (7 1 per cent) Mean V_1Ptf was –0 0088 mm second, SD 0 0110 range 0 to –0 075 mm second Five minutes after exercise mean V_1Ptf had become more negative mean –0 0177 mm second, SD 0 0165, range 0 to –0 075 mm second. According to the definition an abnormal V_1Ptf was found in 176 individuals after exercise (25 4 per cent)

Table I shows the mean values of the blood pressure parameters maximal rate pressure product during exercise (MRPP) and heart volume in individuals with and without an abnormal V_1Ptf All parameters except for heart volume showed slightly higher values in the individuals with an abnormal V_1Ptf at rest None of these differences were significant Individuals with an abnormal V_1Ptf after exercise however showed significantly higher systolic and diastolic blood pressure at rest more increase in systolic blood pressure during exercise, and higher MRPP than in the individuals with normal V_1Ptf

By considering V_1Ptf in subgroups according to various arbitrary levels of blood pressure (Table II) the sole significant result was an inverse correlation between V_1Ptf after exercise and increase in systolic blood pressure during exercise

Relationship between V_1Ptf and fourth heart sound The occurrence of the fourth heart sound was specially sought for in 538 of the 695 normal individuals and was demonstrated by phonocardiography in 272 (50 6 per cent) V_1Ptf at rest was abnormal in 12 of the 272 (4 4 per cent) as compared to 21 of the 266 (7 9 per cent) without a fourth heart sound The corresponding figures concerning V_1Ptf after exercise were 62 (22 8 per cent) and 54 (19 9 per cent) None of these differences were statistically significant

V_1Ptf in latent CHD Table III presents V_1Ptf in relation to the angiographic findings among the 95 individuals who underwent coronary angiography There was no difference between the mean values of these 95 and 695 normals nor a difference in distribution of normal versus abnormal V_1Ptf Neither was there any difference between individuals with normal versus abnormal angiographic findings Hence V_1Ptf could not discriminate between normals and subjects with latent CHD nor between true and falsely suspect cases of CHD

Inter observer variation V_1Ptf was measured in ECG from 790 males at rest and after exercise There was complete agreement between the two

Table I Blood pressure and heart rate parameters and heart volume in groups of individuals classified by V_1Ptf

Parameters	V_1Ptf at rest (mm second)					V_1Ptf after exercise (mm second)				
	> −0 03 (n = 646)		≤ −0 03 (n = 49)			> −0 03 (n = 519)		≤ −0 03 (n = 176)		
	$\bar{x}$	SEM	$\bar{x}$	SEM	p	$\bar{x}$	SEM	$\bar{x}$	SEM	p
SBP (mm. Hg)	124 3	0 6	127 4	2 2	NS	123 8	0 7	126 9	1.3	0 03
DBP (mm Hg)	87 7	0 4	90 7	1 5	NS	87 2	0 5	89 9	0 8	0 005
SBPD (mm Hg)	90 2	0 8	94 6	2 7	NS	89 6	0 9	93.2	1 4	0 03
MRPP (beats per minutes × mm Hg)	35394	181	36146	630	NS	35185	205	36221	320	0 01
Heart volume (mL/M)	393 9	2 0	389 9	8 0		393 8	2 3	393.3	3 7	NS

Abbreviations SBP = systolic blood pressure DBP = diastolic blood pressure SBDP = systolic blood pressure difference (maximal SBP during exercise − SBP at rest) MRPP = maximal rate-pressure product during exercise

Table II V_1Ptf in groups of individuals classified by blood pressure

Blood pressures (mm Hg)		No	V_1Ptf at rest (mm second)			V_1Ptf after exercise (mm second)			
			$\bar{x}$	SEM	p	$\bar{x}$	SEM		p
SBP	< 150	644	−0 0086	0 0004	NS	−0 0175	0 0007		NS
SBP	≥ 150	51	−0 0104	0 0014		−0 0206	0 0024		
DBP	< 100	599	−0 0084	0 0004	NS	−0 0141	0 0007		NS
DBP	≥ 100	96	−0 0111	0 0013		−0 0210	0 0020		
SBPD	≤ 79	209	−0 0078			−0 0150			
	80 99	263	−0 0089		NS	−0 0175		0 02	0 001
	100-119	176	−0 0096			−0 0204			
	≥ 120	47	−0 0096			−0 0209			

Abbreviations as in Table I

observers in 1 001 of the 1 580 measurements of V_1Ptf The total number of abnormal V_1Ptf was 264 and 199 respectively The amplitudes were merging in 1 246 and the duration in 1 049 The differences were mainly due to systematically longer durations measured by one of us (K F) which was obvious at the linear regression analysis made on V_1Ptf at rest V_1Ptf (K F) = 0 993 × V_1Ptf (J E) + 0 0013 r = 0 872 n = 790 Mean V_1Ptf (K F) = −0 0092 mm second SD 0 0113 mean V_1Ptf (J E) = −0 0080 mm second SD 0 0099

Discussion

The present data reemphasize the well known fact that it is hazardous to extrapolate from findings in one population with defined diseases to another comprising apparently normals A $V_1Ptf \leq -0.03$ mm second has been shown to correlate well with various parameters such as left ventricular filling pressure [7,8,9] and left atrial size[11] in individuals with heart disease However the same V_1Ptf was noted in 7 1 per cent of apparently healthy middle aged men at rest and in 25 4 per cent after exercise Hence this sign can hardly be regarded as a valuable sign of heart disease and in particular not of CHD The present study however has shown a weak correlation between the magnitude of V_1Ptf and blood pressure The mechanism may be left ventricular hypertrophy secondary to blood pressure increment and thereby reduced left ventricular compliance left atrial contractions with increased force and thus posterior enlargement of the left atrium leading to a posterior rotation of the P wave in the horizontal plane [1] It is obvious

Table III Number of patients with normal and abnormal V_1Ptf in the various groups classified by EECG* and CA†

Findings by EECG and CA	V Ptf at rest (mm second)		V Ptf after exercise (mm second)	
	> –0 03	≤ –0 03	> –0 03	≤ –0 03
EECG –	646	49	519	176
EECG + CA –	23	6	19	10
EECG + CA +	60	6	49	17

*Exercise electrocardiogram
†Coronary angiography

however that these mechanisms only to a small extent are responsible for the occurrence of abnormal V_1Ptf in the present material In a recent electrophysiological study Josephson and associates[1] have suggested that an interatrial conduction defect may be the underlying cause for the electrocardiographic patterns of left atrial enlargement such as abnormal V_1Ptf This conduction defect may be caused by a variety of factors and possibly by innocent underlying causes in a number of cases according to the present study and thus it may be comprehended as an unimportant anomaly The increase in V_1Ptf seen post exercise may be a physiological response to increased cardiac output

The present study shows clearly that V_1Ptf is of negligible value as a tool for diagnosing asymptomatic CHD These findings strongly support previous findings,[10] and are at variance with the statements by Bethell and Nixon [5]

The reproducibility of the measurements of V_1Ptf is previously found to be satisfactory [9, 10] Although the present study shows complete concordance in the measurements in only two thirds of the cases the inter observer variation was small in most of the remaining cases Hence the method should be acceptable for the clinical use of V_1Ptf

Conclusions

At rest an abnormal V_1Ptf (≤ – 0 03 mm second) is found in 7 1 per cent and post exercise in 25 4 per cent among middle aged males without cardiovascular disease Possibly this finding in individuals without symptoms or signs of heart disease is due to a clinically unimportant anomaly of the interatrial conduction The increase in V_1Ptf post exercise should also be regarded as a normal finding among healthy middle aged men

Summary

In a material comprising 695 males aged 40 to 60 years without cardiovascular disease, the prevalence of abnormal P wave terminal force in V_1 (V_1Ptf) (≤ – 0 03 mm second) at rest was 7 1 per cent, whereas the prevalence five minutes after a near maximal exercise test was 25 4 per cent Abnormal V_1Ptf was associated with a slightly higher systolic and diastolic blood pressure maximal rise of systolic blood pressure, and maximal rate-pressure product during the exercise test The prevalence of abnormal V_1Ptf was not significantly higher in another group of 95 individuals who were angiographied because of strong suspicion of latent coronary heart disease (CHD) according to exercise electrocardiogram

An abnormal V_1Ptf may be considered as a possibly clinically unimportant anomaly in otherwise healthy middle aged men V_1Ptf is not suitable as a tool for the diagnosis of latent CHD

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Clinicopathologic study of the conduction systems in 10 patients with Kawasaki's disease (mucocutaneous lymph node syndrome)

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We found that in cases of Kawasaki's disease there were pathologic lesions in the atrioventricular conduction system.[1] However, at the time we did not study whether these lesions were due to ischemia secondary to coronary stenosis or acute inflammation, itself. The atrioventricular conduction systems were examined in five cases only.

In the present work, pathologic findings in the sinoatrial and atrioventricular conduction systems processed in Kawasaki's disease according to duration of illness at death were studied in the ten autopsied hearts and comparisons between the pathology and the clinical data (ECG) were made.

Materials and methods

The materials were ten unselected hearts obtained at autopsy from Japanese patients diagnosed as having Kawasaki's disease. Eight were clinically typical and two (Case 3 and 9) were not according to the guideline of diagnosis of Kawasaki's disease made by the MLNS Research Committee of the Ministry of Health and Welfare of the Japanese Government† in 1974. All hearts had been fixed in formalin at autopsy. The major three coronary arteries were transversely and serially cut at 0.2 to 0.3 cm intervals and diagrammatically sketched. The heart was incised serially and latitudinally at 0.5 cm intervals and observed macroscopically and microscopically. Age at the time of death, sex, the suddenness of death, and pathologic data of three major coronary arteries and myocardium are summarized according to duration of illness at death in Table I.

Ten tissue blocks containing the atrioventricular (AV) conduction system and eight tissue blocks containing the sinoatrial (SA) conduction system from the ten hearts were removed and serially sectioned at a thickness of 5 microns according to the methods of Lev and associates.[2,3] Every fourth section from each block was stained with hematoxylin eosin and elastic Van Gieson stains. All intervening sections were kept and processed as deemed necessary for additional hematoxylin eosin stained sections or other special stains. For each heart, the average number of histologic sections examined was about 200 to 400.

The clinical record and all available electrocardiograms of each patient were studied.

Results

The pathologic data of sinoatrial (SA) and atrioventricular (AV) conduction systems are summarized according to duration of illness at the time of death in Table II.

In the early acute stage (Case 1—duration of illness from 0 to 9 days), the inflamed and edematous changes without necrosis of the

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Received for publication Jan. 27, 1978.

Accepted for publication Feb. 8, 1978.

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0002-8703/78/1207-44 + 07$00.70/0 © 1978 The C. V. Mosby Co.

Table I Ten autopsy cases with Kawasakı s dısease

Case	Duration of illness	Age/sex	Sudden death	Coronary type	LAD	LCX	RCA	Myo carditis	Coagulation necrosis	Fibrosis
1	9D	10M/m	+	L	N	N	N	+	–	–
2	20D	7M/f	–	R	N	N	S	+	–	–
3	21D	11M/m	+	R	AS	S	AS	+	–	–
4	21D	6M/m	+	R	AS	AS	AS	+	–	–
5	24D	1Yr8M/m	+	R	AS	AS	AS	+	–	–
6	31D	10M/m	+	R	AS	AS	AS	–	+	+
7	48D	11M/f	+	R	AS	A	AS	–	+	+
8	48D	9M/f	+	B	AS	N	AS	–	–	+
9	3M	7M/f	+	B	AS	S	AS	–	–	+
10	M	2yrs/f	+	B	AS	AS	AS	–	–	+

D = days M = m nths Yrs = years m = m l f = female LAD = left a terıor desce dıng artery LCD = left cırcumflex art ry RCA = rıght coronary artery N = macroscop c lly normal artery S = te os s due to thıckened w ll wıth ut aneurysm A = aneurysm wıth ut stenosı of the l men AS = ane rysm wıth severe ste osıs due to thrombus
Coronary types accordıng to the classıfi at on by S hlesıng r et al L = l ft proponder nce R = rıght prepondera ce B = balan ed type
Rupture f LAD
*The stenosıs was less tha 75 pe cent of the l m n

Table II Lesıons of sınoatrıal and atrıoventrıcular conductıon systems ın Kawasakı s dısease

Case	Duration of illness	Sino atrial nodal artery	Sino atrial node	Atrio ven tric ular nodal artery	Cen tral fib rous body	Atrio ventri cular node	Bundle of His	Main bundle branch	Left bundle branch	Right bundle branch	Working muscles of septum			Valvulitis	
											My	Co	Fi	Mitral valve	Tri cuspid valve
1	9D	ns	f	ns	f	d	f	d	d	f	+	–	–	+	+
2	20D	ns	n	ns	d	d	d	d	d	f	+	–	–	++	++
3	21D	ns	n	ns	f	f	n	n	f	n	–	+	–	+	–
4	21D	sa	d	sa	d	d	d	f	f	f	–	+	–	–	–
5	24D			ns	d	f	f	n	f	n	+	–	–	+	+
6	31D	ns	f	ns	f	f	n	n	n	n	–	–	–	–	–
7	48D	ns	n	ss	d	d	d	n	n	n	–	+	–	–	–
8	48D			ss	o	o	n	n	n	n	–	+	+	–	–
9	3M	ss	o	ns	o	n	n	n	n	n	–	+	+	–	–
10	7M	ns	o	ns	o	o	o	o	o	o	–	–	+	–	–
	Total	2/8	5/8	3/10	10/10	9/10	6/10	4/10	6/10	4/10	3/10	5/10	3/10	4/10	3/10

ns = no ste osıs sa = te osıs of the lumen d e to acute angııtıs ss = stenosıs due to scar f = focal (less than 50 per ce t) acute ınflammatory ch nges d = dıffuse (more than 50 per c nt) ute ınfl mm tory ch nges o = ld ınflamm tory hanges n = no fındıngs My = myocardıtıs C = co gul t n necrosıs F = fıbro ıs
Contaın ng the c nectı e tıssues a d muscles buttıng ag ınst cent al fıbrous body
Bleedıng (gon l h ge or artıfact)

conductıon cells were conspıcuous ın the AV conductıon system (Fıg 1) The most numerous cells were neutrophıls wıth lymphocytes Plasma cells eosınophıls and monocytes were occasıonal ly evıdent The ınflammatory cells tended to be more concentrated at the perıvascular area of the mıcrovessels and the borders of the conductıon system as ıt abuts agaınst the adjacent tıssue In the AV nodal artery acute angııtıs wıthout steno sıs was noted Both mıtral and trıcuspıd valves had a focal endocardıtıs In the SA node and around the neıghborıng ganglıon the ınflammato ry cell ınfıltratıon was focally and extensıvely evıdent

In the most severe acute stage (Cases 2 to 6—duratıon of ıllness from 21 to 31 days) severe edematous changes wıth fıne fıbrosıs ın the perı vascular area of the mıcrovessels and the exten sıve compressıon of the conductıon cells wıth degeneratıon and necrosıs were evıdent ın AV

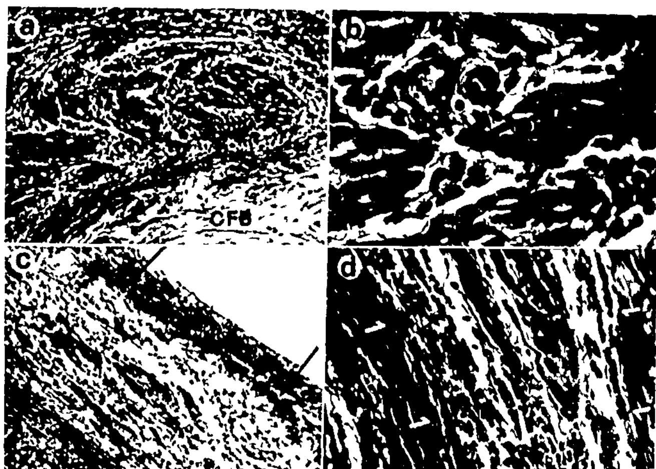


Fig 1 Atrioventricular (AV) and sinoatrial (SA) conduction systems of Case 1 in the early acute stage *a* diffuse inflammation of the AV node *CFB* = central fibrous body (Hematoxylin and eosin stain original magnification 10 power × 10) *b* a magnification of *(a)* Perivascular cell infiltration consisted of leukocytes and lymphocytes (Hematoxylin and eosin stain original magnification 40 power × 10) *c* inflammation of stem of the left bundle branch → means the left bundle branch (Hematoxylin and eosin stain original magnification 10 power × 10) *d* inflammation of the right bundle branch → means the right bundle branch (Hematoxylin and eosin stain original magnification 20 power × 10)

conduction system in all five cases (Table II and Fig 2) The numerous inflammatory cells consisted of lymphocytes atypical lymphocytes plasma cells, large mononuclear cells fibroblasts and fibrocytes The above changes were noted throughout all of AV conduction system especially in the approach of the AV node where the inflammation was noted in all cases Inflammation of the bundle branches was severe in the stems and mild in the peripheries The greatest inflammatory changes were detected in the connective tissues fatty tissues and atrial and ventricular septal muscles abutting against the central fibrous body (Fig 2) There was no evidence of coagulation necrosis of AV conduction cells although coagulation necrosis was frequently detected in the ventricular septum (Table II) In addition to endocarditis of the valves inflammation in the root of the valve was frequently noted (Table II) In Case 2 severe panvalvulitis occurred (Fig 2) Angiitis with severe stenosis of the lumen occurred in the AV and SA nodal arteries (Table II) In the SA node and neighboring ganglions inflammatory changes were focally noted in three of four cases

In the end stage (cases 7 to 10—duration of illness from 48 days to 7 months) old and inflammatory changes consisting of the perivascular fibrosis of small or microvessels and fatty infiltration were conspicuous in both AV (Cases 8 and 10) and SA (Case 9) conduction systems (Figs 3 and 4) although the same evidence as in the acute stage was noted in Case 7 There was no evidence of any considerable loss of conduction cells coagulation necrosis or massive fibrosis in the AV and SA conduction systems In three out of four cases the elastic tissue of the collagenous extension of the central fibrous body was definitely increased Acute valvulitis disappeared Severe stenosis with recanalization due to a thickened wall secondary to scar formation was noted in AV and SA nodal arteries (Table II and Fig 4)

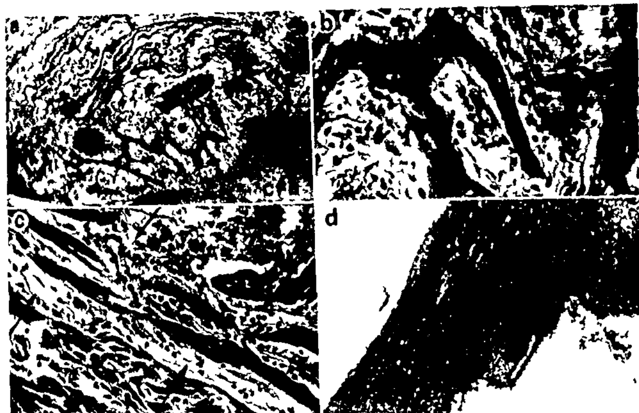


Fig 2 Atrioventricular (AV) conduction system of Case 2 in the most severe acute stage *a* inflammation of the AV node with severe compression of the conduction cells due to perivascular edema and cell infiltration Severe inflammation was noted in the central fibrous body *(CFB)* → means the AV node (Hematoxylin and eosin stain original magnification 5 power × 10) *b* a magnification of *(a)* There was no evidence of diffuse necrosis of the conduction cells despite severe compression Perivascular cellular infiltration consisted of mononuclear cells fibroblast and fibrocytes (Hematoxylin and eosin stain original magnification 40 power × 10) *c* inflammation of the right bundle branch ——→ means right bundle branch (Hematoxylin and eosin stain original magnification 20 power × 10) *d* the mitral valve with panvalvulitis (Hematoxylin and eosin stain original magnification 5 power × 10)

Correlation between electrocardiogram (ECG) and pathology in the conduction systems ECG data on the conduction disturbances or ectopic beats are summarized in Table III An ECG had not been taken in Cases 4 and 5 therefore such data were only available for eight cases Prolongation of PQ interval was noted in four cases (Cases 2 3 8 and 10) In Cases 2 and 3 an acute pathologic lesion of the AV conduction system was detected In Cases 8 and 10 the pathologic lesions were old and healed changes (Fig 3 and Table II) These PQ prolongations appeared in the acute stage and disappeared after the 24th day of illness in Case 8 and after the 18th day of illness in Case 10 (Table III and Fig 3) Acute pathologic lesions were probably present in the acute stage when PQ prolongations were evident A complete AV block was seen in the ECG one day prior to death in Case 7 Diffuse lesions of the acute stage were discovered in the AV node and bundle of His As there was evidence of diffuse coagulation necrosis in the high posterior of the ventricular septum, the ischemia would have superimposed the inflammatory changes of the AV conduction system Supraventricular tachycardia was present on the day of death and pathologic lesions were evident in both AV and SA conduction systems in Case 6 In Case 9 no pathologic changes of the AV conduction system or conduction disturbances in the recurrence ECG were noted The incompatibility between pathology and ECG was noted in only one case (Case 1) in which there were acute inflammatory changes of the AV conduction system and yet no evident abnormality in the ECG (Fig 1 and Tables II and III)

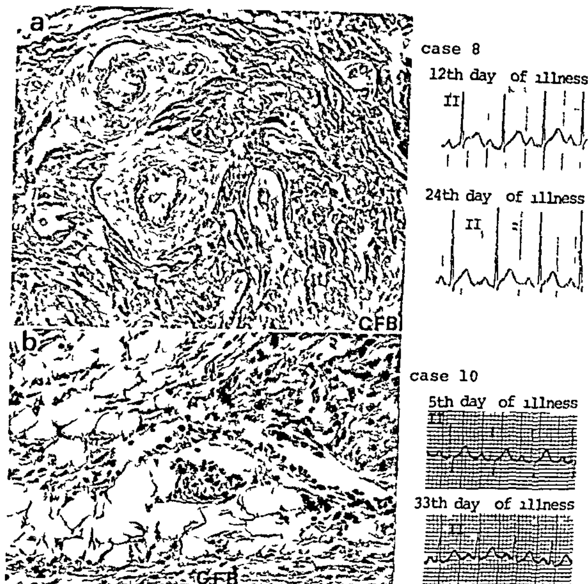


Fig 3 Atrioventricular (AV) conduction system in the end stage and the electrocardiograms (ECG) *a* perivascular fibrosis without considerable loss of the conduction cells in the AV node of Case 8 CFB-central fibrous body (Hematoxylin and eosin stain original magnification 20 power × 10) *Right* the ECG revealed PQ prolongation (PQ interval = 0 16 sec upper limits of normal control = 0 125 sec) on the 12th day of illness and normal PQ interval on the 24th day of illness *b* fatty infiltration in the bundle of His of Case 10 *CFB* = central fibrous body (Hematoxylin and eosin stain original magnification 20 power × 10) *Right* The ECG revealed PQ prolongation (PQ interval 0 14 sec upper limits of normal control = 0 135 sec [5]) on the 5th day of illness and normal PQ interval on the 18th day of illness

The pathologic lesions of SA conduction system were subclinical in three of four cases (Cases 1, 9 and 10) and in Case 6 there was evidence of a supraventricular tachycardia In the other three cases (Cases 2 3 and 7) there was no pathologic lesion, and no sinus arrest second SA block, or ectopic beats Sinus tachycardia was noted in all except Case 6 (Table III)

Discussion

Kawasaki s disease cannot be pathologically and clinically distinguished from infantile periarteritis nodosa at present [1, 6, 7] According to one case report of infantile periarteritis nodosa in which the subject died after 6 months of illness [8] the conduction systems gave evidence of pathological findings much the same as found reported in the end stage of our present work

It is not surprising that the lesions were discovered in nine of 10 cases in the AV conduction system and in five of eight cases in the SA conduction system in autopsies of Kawasaki s disease The death rate in cases of Kawasaki s disease is 1 to 2 per cent [9]

The pathologic lesions could be differentiated from myocardial infarction, as the lesions began from edema and cell infiltration in the early and acute stages without coronary stenosis (Cases 1



Fig 4 Sinoatrial (SA) and atrioventricular (AV) nodal arteries with severe stenosis with recanalization due to scar formation in the end stage *a* the SA nodal artery of Case 9 with fatty infiltration in the SA node (Hematoxylin and eosin stain original magnification 20 power × 10) *b* the AV nodal artery of Case 7 (Hematoxylin and eosin stain original magnification 20 power × 10)

Table III Conduction disturbances or ectopic beats in ECG according to duration of illness

Case	Duration of illness				At death
	10 days	*20 days*	*40 days*	*3 months*	
1	0 11 (180)				9 days
	0 16 (180)	0 13 (180) 0 14 (140)			20 days
3	0 14 (130)	0 14 (150) 0 17 (125)			21 days
4	no ECG				21 days
5	no ECG				24 days
6			SVT		31 days
7			CAVB		48 days
8	0 16 (140)	0 13 (170) 0 12 (135)	0 11 (170)		48 days
9	0 10 (180)	0 11 (175) 0 10 (155)		0 10 (135)	3 months
10	0 14 (140) 0 14 (150)	0 13 (105) 0 13 (95)	0 10 (150) 0 12 (100)	0 14 (125)	7 months

N mbers outs de of p ret theses = PQ int rv l (sec) n mbers within p rentheses = h art rates und lined numbers = prolo gation of PQ interval
SVT = supra ntricular tachy rdi CAVB = ompl te atr o ntricul r block
One dav prio to de th
Th d y of de th
*Ten days pri r t death
Fo irteen days prio to d ath
Fi m ths prior to de th.

and 2) and disappeared about the 48th day of illness leaving behind a mild fibrosis of the peri vascular area and mild fatty infiltration without considerable loss of conduction cells There was no evidence of coagulation necrosis of conduction cells in subjects with severe stenosis of the coro nary arteries Therefore it is concluded that the pathologic lesions of the conduction system are acute and inflammatory even if the ischemia is superimposed on the inflammatory changes in those with severe coronary stenosis

Inflammation of the central fibrous body the neighboring tissues atrium and valves was frequently evident and as such was analogous to that seen in acute rheumatic fever [10] Aschoff bodies were not detected in our series

All five cases with AV blocks had pathologic lesions in the AV conduction system Cases 8 and 10 in which PQ prolongation had appeared in the acute stage and disappeared in the end stage had old and healed changes in the AV conduction system Five of seven cases with pathologic lesions in the AV conduction system also had AV blocks in the ECG One of two other cases had

supraventricular tachycardia Case 9 with no pathologic lesion had no AV block either in the acute stage or in the end stage Our findings indicate that the ECG is a sensitive indicator of lesions of the AV conduction system Especially there was a good correlation between PQ prolongation and acute inflammation of the AV conduction system in Kawasaki's disease

It has been reported that PQ prolongation appears frequently in the acute stage but second or third degree AV blocks were rare in Kawasaki s disease[11 1] So also was diffuse inflammation of the AV conduction system This is attributed to the lack of diffuse necrosis of the conduction cells in the interstitial myocarditis of Kawasaki's disease

In view of the long term prognosis of Kawasaki s disease, it is significant that the stenosis of the SA or AV nodal artery due to scar formation remains after disappearance of the acute angiitis This stenosis also remains in the three major coronary arteries

Summary

Clinicopathologic study of the conduction systems was done on ten hearts obtained at autopsy from patients with Kawasaki s disease

The pathologic lesions were discovered in the atrioventricular (AV) conduction system in nine out of 10 cases and in five of eight cases in the sinoatrial (SA) conduction system The lesions of the AV conduction system were classified according to duration of illness at death Early acute stage (0 to 9 days) was characterized by inflammation with cell infiltration and edema without coronary stenosis The most severe acute stage (21 to 31 days) was characterized by severe compression of conduction cells without the diffuse necrosis due to severe perivascular edema and cell infiltration In the end stage (48 days to 7 months), old changes with perivascular fibrosis and fatty infiltration without considerable loss of the conduction cells were noted Coagulation necrosis of the conduction cells was not evident despite the severe coronary stenosis Lesions in the conduction system are therefore acute and inflammatory

Pathology and electrocardiogram showed a good correlation in seven of eight cases PQ prolongation was a sensitive indicator of acute inflammation of the AV conduction system in the present study

Thanks are due to Drs T Kawasaki R Okada F Hazama K Nishioka and T Asai for pertinent discussions K Tsuchida for technical assistance and M Ohara for assistance with preparation of the manuscript.

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Experimental and laboratory reports

Exercise tests, atrial pacing and myocardial lactate extraction in relation to coronary arteriography in young patients with angina pectoris

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Since the introduction of selective coronary arteriography conservative opinions have been expressed concerning the need for and use of coronary arteriography [3] The prognostic implications of this examination and the diagnostic approach to coronary artery disease have been emphasized in comparison with the risks which have diminished with adequate facilities and greater experience [4] Myocardial ischemia can be diagnosed on the basis of a typical history of angina pectoris even in the absence of any further evidence In many situations however there may be cause for more extensive investigations from a purely medical standpoint or because of the patient s personal needs or the requirements of the community The use of exercise studies and atrial pacing and even myocardial biopsies does not exclude the significance of coronary arteriography It has also been concluded that with the use of coronary arteriograms and left ventricular biopsy alone it may be extremely difficult to separate patients aged over 40 years with left ventricular dysfunction due to ischemic heart disease from tho e with cardiomyopathy Thus arteriographic studies provide a means of fulfilling the need for adequate anatomical diagnosis even in younger persons and when other methods of investigation are also used The opinion that arteriographic evaluation is not justified in patients presumed to be at low risk is correct But when the symptoms jeopardize the patient s working capacity investigations must be carried out in depth even in younger patients not only for the diagnosis per se but also in order to decide upon the appropriate treatment and rehabilitation In this study the methods used *in the* evaluation of possible ischemic heart disease have been applied to young patients with angina pectoris (1) to get information about possible changes in coronary arteriograms (2) to compare these with the findings in other examinations and (3) to disclose if there are any specific divergent features behind the angina pectoris symptoms in young patients

Methods

Patients All 55 presenting patients forming this series were aged 40 or less and had been referred for examination because of angina pectoris A basic examination was performed and other possible causes of the symptoms were excluded in the outpatient department The patients with *congenital* or valvular heart disease or findings consistent with previous myocardial infarction and similarly those with hypertension anemia or diabetes are excluded from this series Biochemical parameters including blood lipids and glucose tolerance were determined Those patients in whom angina pectoris then seemed probable were sent for a cardiological examination The distribution of the patients by sex and age is presented in Table I The symptoms were recorded before the physical examination or any other measures had been undertaken The physical activity involved in the patient s everyday work was also evaluated [3] since one indication for a thorough

Fro n the Cardiovasc l Di is n Department f Internal Med cin U ersity of Oul Oulu Finl nd

Recei ed f public tion J 12, 19 8
Accepted f publ tio M r 31 19 8

Repri t requests Dr J T kku en C rdiovascular D visi n D pt of I ternal Med U i rs ty f Oulu SF 90??0 Oulu 22 Finla d.

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Table I Classification of the 55 patients of age 40 or less comprising the present series by sex and age

	Age groups (yrs)				
	21 25	*26 30*	*31-35*	*36 40*	*Total*
Women	3	4	8	18	33
Men	3	3	8	8	22

examination had been their incapacity to perform their daily work Sedentary work in a bank or office or some comparable position was assigned to the first category light work including more walking and some lifting or moving of heavier objects formed the second, heavy work taken to include physically strenuous tasks in a factory or warehouse formed the third, while the fourth category, that of very hard workers, comprised mainly longshoremen, farmers, and lumber jacks

Exercise ECG The test was conducted using an electrically braked bicycle (Godart Statham NV Bilthoven, Holland), with a load of 30 W initially increasing by 10 W /minute for women and 15 W /minute for men The exercise was continued until the patient was exhausted or until anginal symptoms prevented further pedal ling A conventional 12 lead ECG was taken before exercise and at two and five minutes afterwards The patients were monitored throughout, the electrodes for which were placed according to a modified CM_5 system[14] on the manubrium sterni, high sacrum, and correspond ing to the ECG Lead V_5 to get minimal distur bance from muscle function A recording was made every minute at a paper speed of 50 mm / sec the cuff blood pressure also being measured A depression of 0 5 mm or more in the ST segment was regarded as pathologically signifi cant[15] Serious arrhythmias were taken as natural indicators to stop the exercise A three channel Elema Schonander Mingograph 43 was used in the exercise and pacing studies

Blood sampling and lactate determination A Zuckers catheter[16] was introduced into the coro nary sinus via the cubital vein If needed a lateral x ray tube was used The catheter was positioned in the coronary sinus as far as possible in such a manner that the blood sampling was not prevented which would have meant wedging of the vein This technique was used in an attempt to obtain as adequate and comparable samples as possible for the measurement of lactate concen trations in the blood draining the left ventricle This position also had a suitably low threshold for pacing by means of a Medtronic Model 5837 pulse generator Arterial samples were collected simul taneously with coronary sinus sampling The blood samples were immediately denatured with five volumes of ice cold 0 6 N trichloracetic acid in closed tubes in a blender and placed in an icebath for transportation to the laboratory followed by immediate analysis by an enzymatic method[17] The normal value for lactate extrac tion, which is the difference between the arterial and coronary sinus concentrations calculated as a percentage of the former, is over 10 per cent[18] A lower extraction or a net accumulation of lactate in the coronary sinus blood was regarded as pathological in accordance with references in the literature

Atrial pacing An intravenous injection of 0 6 mg of atropine sulphate was used to prevent any interference with Wenckebach s phenomenon After the injection the heart rate was brought up to 170/minute in about 30 seconds Blood samples and a 12 lead ECG were taken before pacing and at 2 and 4 minutes Pacing lasted for 4 minutes in all Blood samples and electrocardiograms were then taken at 3 and 5 minutes after the cessation of pacing A three lead ($V_{1,6}$) ECG sample was recorded every minute during pacing and during the transition from pacing to sinus rhythm[1] The recordings were satisfactory for a comparison to be made of any ST segment changes during and immediately after the pacing

Coronary arteriography Judkins technique was used for coronary arteriography[2] special care being taken not to introduce the catheter too far into the artery in order to avoid irritation and spasms A good backflow to the aorta was regarded as an indication of good catheter posi tion Two to 8 ml of contrast material (Urografin 60 per cent) was injected by hand Ostial stenosis was evaluated from a nearby ostial injection or aortography or from clear and immediate ostial wedging of the catheter The biplane cineangio graphy instrumentation consisted of two Philips Maximus 100 roentgen generators with an XG 7002 cinepulse apparatus and Philips HQ type image intensifiers with Arritekno R 90 cameras and a Philips Angio Diagnost table The biplane cineangiographies were taken in the frontal and 30 degree right anterior oblique positions with a

film speed of 50 frames/sec All angiographies were evaluated by three independent cardiologists and disagreement was settled by consultation If a spasm of the coronary artery was suspected nitroglycerine was used immediately in a new arteriography and the exposure was taken about two minutes later The diameter of the stenosis of the coronary artery was compared with that of the same artery proximal to the narrowed segment and was expressed as a percentage of the latter A significant change was held to be one involving a narrowing of 50 per cent or more a degree of stenosis which is termed here obviously pathological The dominance of a coronary artery was determined from the lateral films Vascularization was balanced if the right coronary artery and the circumflex branch shared approximately equal parts of the posteroinferior part of the heart In other cases one of these could be called dominant Minor changes involved a narrowing of less than 50 per cent or a vessel or main branch of general small size The loading of the myocardial small vessels with contrast material and the slow disappearance of this were also recorded The nomenclature recommended by Kretschmann and Kaltenbach[7] is used in abbreviations

Results

Most of the patients fall into the age groups 31 to 35 and 36 to 40 (Table I) The female patients comprise more than half of the total most of them being in the age group 36 to 40 years There is a clear difference between Tables I and II in that relatively more men are doing heavy or very heavy work Housework was not included in the evaluation Two thirds of the women (23 out of 33) were employed in sedentary or light work but these still experienced anginal symptoms at work or at home in the evening In Table III the patients are grouped according to the findings in coronary arteriography versus family history type of symptoms and sex age and the duration of the symptoms The men with obvious coronary changes are of greater age and have a significantly shorter duration of the symptoms than the women with coronary changes or the men with normal arteriograms More prolonged anginal symptoms are found among the patients with pathological arteriograms in relation to their number Early coronary disease means a coronary disease in the immediate members of the family and includes only men aged less than 50 years and women aged less than 60 years since angina pectoris becomes very common with advancing age in Finland[2, 21] Even with this exclusion there is a high evenly distributed incidence of angina pectoris in the near family in the young angina pectoris patients if the findings in coronary arteriography are ignored Although angina pectoris was a criterion for admission to this series five women did not have all their attacks in relation to physical stress so that only 23 women without coronary changes have a typical history of effort angina

In the laboratory tests all patients had normal glucose tolerance Of lipids only cholesterol and triglycerides were determined The range of cholesterol values in five women with hypercholesterolemia was 277 to 308 mg/dl and respectively in seven men it was 289 to 461 mg/dl (normal below 270 mg/dl) The triglyceride values were evaluated in one woman (257 mg/dl) and in four of these men it was 230 to 354 mg/dl when the upper limit of normal is 150 mg/dl All these patients except one man were in the oldest age group Three of the men had narrowings in the coronary arteriograms which means that half of the men with obvious coronary changes had

Table II Patients classified by sex and physical strain of their work

	1	*2†*	*3‡*	*4§*
Women	8	15	10	–
Men	1	5	11	5

Sedentary sitting work
†Light work moving and lifting
‡Heavy work–factory type work
§Very heavy work–farmer lumberjack

Table III Findings in coronary arteriography in relation to the history of angina pectoris

	Pathological arteriogram		*Normal arteriogram*	
	Women	*Men*	*Women*	*Men*
Sex and number	5	6	28	16
Mean age (years)	3[illegible].2	35.5	35.2	[illegible]0.2
Duration of symptoms (years)	2.4	1.7	3.2	3.9
Early coronary disease in family	4	3	14	8
Effort angina	5	6	23	16
Prolonged angina	3	3	12	5

Table IV Type, location, and degree of minor changes in six patients with a coronary arteriogram deviating from normal, but without significant stenosis

Sex and age	*RC**	*LC*	*LAD & LD*	*LCx*	*Dominance*
F 40	–	kinking	–	–	Balanced
F 39	small	–	–	–	LC
F 40	small	–	below 50	–	LC
F 26	–	–	–	small	RC
M 32	small	–	–	–	LC
M 39	small	–	below 50	–	LC

RC = right coronary LC = left coronary LAD = left anterior descending branch LD = left diagonal branch LCx = left circumflex artery

Table V Location and degree of stenotic coronary changes in 11 patients in whom a clear change was found in arteriography The balance between the coronaries is also recorded

	Stenosed artery and degree of stenosis (in %)				
Sex and age	*RC**	*LC*	*LAD & LD*	*LCx*	*Dominance*
F 33	over 50	–	–	50	RC
F 36	over 50	–	–	–	Balanced
F 33	70	short	small	small	RC
F 38	70	short	–	–	RC
F 21	50 & 70	–	–	–	LC
M 39	over 50	–	75	below 50	Balanced
M 34	over 50	–	50	–	RC
M 39	75	–	over 50	–	RC
M 28	small 75	–	–	–	LC
M 35	75	–	LD 100	–	RC
M 38	100	–	–	small	LC

RC = right coronary LC = left coronary LAD = left anterior descending branch LD = left diagonal branch LCx = left circumflex artery

hypercholesterolemia The results of coronary arteriography are presented in Tables IV and V According to the criteria used, there are five women out of 33 and six men out of 22 with a clear narrowing of more than 50 per cent in one or more arteries, while minor changes were found in four women and two men An obvious two or three vessel stenosis was found in four of the six men mentioned Only one of the women had two vessel stenosis Patients with small coronary arteries are to be found among both those with and without stenotic changes All of these also had a slow clearance of the contrast material from the myocardium One woman had a functional kinking of the left main coronary artery near the first bifurcation In general the right coronary artery was affected more frequently than the left in this population Two total occlusions were found, both in men, one in the diagonal branch of the left coronary artery Both men had a normal resting ECG and the patient with the occlusion of the right coronary also gave a normal finding in the lactate study, but had a very low exercise capacity without ECG changes His maximal heart rate was only 98 and in two minutes he developed angina pectoris with pallor and dizziness The other man with the obstructed ventricular branch of left coronary artery had pathological findings in the exercise ECG pacing ECG and lactate study, as well as an exercise capacity for a heart rate of 115 in 3 minutes The right coronary artery was dominant in six out of the eleven patients with obvious coronary changes No clear collaterals from the main branches of one coronary artery to the other could be seen

The pathological and normal findings in coronary arteriography are presented in Table VI in relation to the results in other tests Most of the patients with stenotic findings also had a clear pathology in the dynamic clinical tests The women with normal arteriograms, on the other hand had pathological finding in more than two thirds of the tests The men with normal arteriograms also had more normal results in the exercise ECG and lactate test, but in the pacing ECG more of them gave an ST segment depression like the women with normal arteriograms The data in Table VI enable the sensitivity and specificity of the exercise pacing and lactate tests to be calculated by considering the coronary arteriography as the definitive diagnostic procedure The results are presented as percentages in Table VII The sensitivity of these tests in the young patients with angina pectoris appears on this basis to be very high, with the pacing ECG the least specific The specificity of the tests carried out on women was one half or two thirds of that in the tests on men

The results of the various tests in relation to the coronary arteriogram are presented in Figs 1 and 2 Among the 11 patients with stenotic coronary changes there were five who had pathological results in all three functional tests as seen in Fig 1 In one man only the exercise ECG was

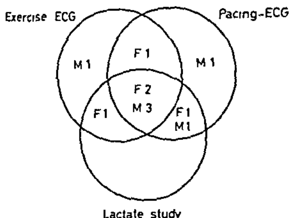


Fig 1 Venn diagram for the pathological findings in the exercise ECG pacing ECG and lactate study in patients with obvious coronary changes in coronary arteriography M = men F = women

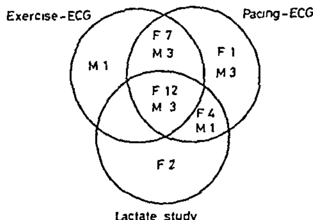


Fig 2 Venn diagram for the pathological findings in the exercise ECG pacing ECG and lactate test in patients with minor changes or normal findings in coronary arteriograms Seven patients with normal results are excluded M = men F = women

Table VI Pathological and normal findings in patients with and without obvious stenotic coronary changes in the arteriograms Seven patients had normal results throughout

	Pathological arteriogram		*Normal arteriogram*	
	Women	*Men*	*Women*	*Men*
Exercise ECG				
Pathological	4	4	19	7
Normal	1	2	9	9
Pacing ECG				
Pathological	4	5	24	10
Normal	1	1	4	6
Lactate test				
Pathological	4	4	18	4
Normal	1	2	10	12

Table VII Calculated sensitivities and specificities of the exercise ECG pacing ECG and lactate test according to the criteria used The finding of a stenosis of more than 50 per cent in a coronary lumen in the arteriogram is taken as indicative of significant coronary disease

		Sensitivity %	*Specificity %*
	Total	72 7	40 9
Exercise ECG	Men	66 6	56 3
	Women	80 0	35 0
	Total	81 8	27 0
Pacing ECG	Men	83 3	37 5
	Women	80 0	14 3
	Total	72 7	47 7
Lactate test	Men	66 6	68 8
	Women	80 0	38 5

pathological and in another only the pacing ECG was pathological Both had a moderate working capacity but developed angina pectoris that prevented further pedalling and both were farmers who worked during wintertime as lumberjacks The elder aged 34 years had the principal stenosis in the right coronary artery but also had minor narrowings in the left anterior descendent branch while the younger aged 28 years had a long stenotic section of 75 per cent that comprised the first third of the right coronary artery He developed a second degree atrioventricular block during exercise and had a history of faintings with angina pectoris in the course of heavy work during previous years Most of the patients with coronary changes had pathological results in the lactate study but discrepancies in their exercise and pacing ECGs Fig 2 presents the pathological results in the patients with minor coronary changes or normal coronary arteriograms Most of them have pathological findings in the pacing ECG All three tests were pathological in 15 out of the 37 patients included in this diagram Seven patients are not included and must be regarded as true negatives because all their results were normal The concept of serial testing deems a person positive only if he gives positive results in the whole series This would suggest according to Fig 1 a sensitivity in detecting coronary changes of 50 per cent in men and 40 per cent in women for these physiological tests On the other hand, the power of serial tests to detect persons without

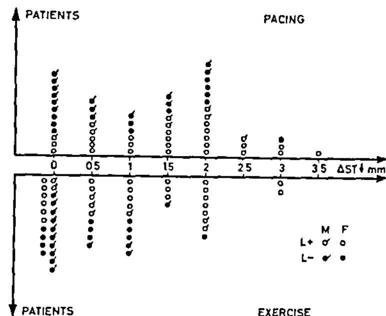


Fig 3 ST segment depressions in patients with pathological *(open circles)* and normal *(closed circles)* results in lactate tests by sex

coronary changes is apparently good in men, for the specificity, as calculated from the data in Fig 2 is 80 per cent for men in this case, whereas for women it is only 55 5 per cent The difference is significant in clinical practice

The ST segment changes in exercise and pacing tests are presented in Fig 3 in relation to the findings in the lactate study There is no clear separation of patients with regard to the degree of ST depression and the result in the lactate test The woman with a 3 mm ST depression in pacing had only an 0 5 mm depression in exercise and normal lactate response but she had a narrowing of 70 per cent in the right coronary artery and her exercise time was only 2 minutes to angina pectoris that she also felt during pacing

Two men and two women had evidence of mitral valve prolapse One of the men had occlusion in the first third of the right coronary artery and the other one had a stenotic first third of the same vessel One of the women had a small right coronary artery and a narrowing of less than 50 per cent in the left anterior descending branch She had pathological results in ECG and lactate tests The other woman had normal arteriograms and only ST depressions in pacing These findings were confirmed by left ventriculograms and echocardiography

Discussion

In epidemiological studies of angina pectoris in Finland the prevalence in the age group 30 to 34 years in men was 0 4 per cent and in the age group 35 to 39 years it was 1 2 per cent The corresponding figures for women were 1 6 and 2 6 per cent respectively, or about two to three times higher than for men Our study population was selected after a tight clinical scrutiny that excluded the possible extracardiac causes of chest pain The patients considered to have typical angina pectoris and who found themselves unable to do their work because of the symptoms were submitted with their consent to a thorough cardiological examination Of the 71 patients referred to cardiological evaluation four did not accept the invasive procedure four were excluded because of diabetes and eight patients were excluded because of hypertension The exact prevalence of patients with this degree of angina pectoris cannot be adequately presented in relation to the epidemiological numbers but at any rate they form a minority in the young age groups The relation of men to women corresponds to the relation of the prevalence percentages in the referenced epidemiological study The number of patients and findings increase with age from 20 to 40 years (Table I) which is in agreement with epidemiological clinical and anatomico pathological findings in Finland ' In the patients studied the physical stress of their work did not bear any clear relation to the existence of the symptom but most of the typical coronary changes were found in the people who did heavy work Six women and seven men of the study group did smoke 10 to 20 cigarettes a day One man and one woman of these had coronary

changes At the time of the examination no one of the women was taking estrogen containing medication

The sensitivity of exercise testing is higher in women but the specificity markedly better among men (Table VII) The high prevalence of false positive exercise ECG findings among healthy women and also symptomatic patients has been previously documented[25,27] The ability of the lactate test to distinguish men without any significant coronary changes is evident and also the sensitivity of lactate test is in agreement with previous publications [18] The significance of the coronary arteriography has been questioned but it is clear in several patients of this study when both a negative exercise test and a negative lactate test made the diagnosis doubtful In two men and one woman an occlusion or a narrowing of the right coronary artery was found but they had only a very low exercise capacity with a low angina pectoris threshold in other tests Consequently we must be ready to go through the diagnostic algorithm recently presented by Hurst and King[28] in a thorough manner even in the case of young patients In addition to the classical angina pectoris at times of effort prolonged chest discomfort after physical stress is also an indication for a careful examination (Table III) In men the symptoms seem to be clearer and led more directly to an examination in our series of patients

Another important fact is that even though the women had more normal findings neither mean age nor family history nor the type or duration of the symptoms served to separate those with coronary changes from others A large proportion of the women were employed in light work and of the five women with pathological findings in coronary arteriography only one was a heavy laborer but still they had anginal symptoms even doing light work More than 60 per cent of women with normal arteriograms showed lactate production during pacing but in men the situation was reversed a result that has been found previously This may suggest that angina pectoris in young people with no significant coronary changes is perhaps an entity distinct from classical coronary disease even if coronary disease exists in these patients A few clear pathological findings in the major coronary arteries did emerge in these young patients and this argues in favor of the findings obtained in pathologico anatomical studies[21,3] and clinical studies [4] that these patients actually have large vessel disease The criteria adopted for the definition of pathological results were those commonly used and these have been evaluated on many occasions[11] mostly in connection with patients who are older than the present series and who had more evidence of ischemic heart disease before coronary arteriography Our selection criteria imply a minimum of selectivity with regard to the ECG changes at rest The 0 5 mm depression in the ST segment upon exercise is very sensitive as is shown in Table VII The sensitivity percentages obtained in the men are within the range noted in previous studies using an ST depression of 1 mm [2,3] If the sensitivity data computed for an ST segment depression of 1 mm or more in the exercise test for men are 66 7 and for women are 60 0 the specificity percentages are 68 7 and 57 1 respectively The corresponding sensitivity values in pacing tests are for men 50 0 and for women 60 0 the sensitivity percentages being 37 5 and 21 4 respectively Compared to the data in Table VII a significantly better result is reached only in the specificity percentages for women in the exercise test The high sensitivity of the criteria used here is reflected in the low percentages of specificity This logical situation is tolerable in the exercise ECG but in the pacing ECG the 0 5 mm criterion is evidently useless On the basis of results presented in Fig 3 we are thus inclined to agree with previous investigators who found that a depression of 2 to 4 mm correlated best with a pathological result in the lactate extraction test[32] Three of our six male patients with coronary changes had an ST depression of 2 to 3 mm and two had an ST depression of 0 5 to 1 mm while one ga e r o ST depression either during or after pacing a result consistent with findings in older patients[2] The 16 men with normal coronary arteriograms and normal lactate extraction also had fewer ST changes but these findings do not separate them The pathological findings in the exercise ECG and lactate test correlate well from the qualitative point of view in individual patients but in some situations the lactate extraction test is missleading because the coronary sinus drains the blood mainly from the left ventricle[1] Three examples have been presented where changes in the right coronary artery were connected with low ergometric capacity and angina pectoris at a low heart rate In the case of

patients with this degree of angina, it is proper to obtain a coronary arteriogram rather than to require a new exercise test [4] The low specificity of the exercise ECG the pacing ECG and the myocardial lactate study for the indication of ischemia in young women is also evident here as in previous reports, where false positive results have been obtained in 30 to 67 per cent of women *with angina pectoris* [4, 3, 28] or without [5] The exact nature of the coronary changes recorded in arteriography remains open In most cases they seem to be identical with the findings in older patients with atherosclerosis In one woman aged 22 the two narrowings indicated in the right coronary artery are difficult to explain on this basis Other possibilities are infectious lesions or some systemic disease that could not be identified in our study [11] The case of those patients who had a very small coronary artery without any narrowings is also highly interesting The other coronary artery was naturally the dominant one but no collateral circulation was found A loading of the myocardium with contrast material, which was slow to disappear, was also typical [14] It has been proposed that venous drainage or a stagnation on the venous side could be a notable factor in the ischemic heart disease [15] Our findings are compatible with this The pathological changes were ostial in two male and two female patients which is consistent with autopsy findings on young people who have died acutely [23] These patients also presented practical problems in the examination as they were prone to develop bradycardia and various arrhythmias when the catheter was introduced into the ostium of the artery The ostial narrowings were all found in the right coronary artery as were most of the narrowings found in this series but this may be only a coincidence On the other hand the right coronary artery was also dominant in these patients and this may possibly be a cause of the accentuated symptoms that led the patients to this examination The venn diagrams in Figs 1 and 2 show that about half of the men and women with coronary changes as well as half of the women with no coronary changes had all other three test results appear pathological The men with normal coronary arteriograms had fewer pathological changes also in the other tests Of the four patients with mitral prolapse three had abnormalities in the right coronary artery in agreement with some[3] but not with most of the results [37] Totally normal arteriographic findings and dynamic test results were registered in two women and in five men The exact nature of ischemic heart disease with open coronary arteries still remains unexplained,[3] but there is considerable evidence in favor of small vessel disease [3]

Other possibilities are metabolic disturbances or abnormal reactivity of the coronary vessels since no clear morphological disease of the small myocardial arteries has yet been found in biopsies [10] The generally known ominous nature of chest pain related to physical stress in any case seems to lead patients in Finland to seek all possible help in explaining their symptoms The follow up of these patients after the thorough medical survey seems to be the only way of furnishing such an explanation and providing guidelines for the physician

Summary

An exercise ECG and atrial pacing with a simultaneous study of myocardial lactate metabolism were used in conjunction with coronary arteriographies for the examination of 33 women and 22 men aged 40 or below whose working capacity was impaired by angina pectoris Most of the patients fell into the age group 36 to 40 The men with coronary changes had come for examination in a shorter time than other patients Coronary artery narrowings were found in five women and six men The findings in other tests were pathological with greater frequency in patients with coronary stenosis When evaluated on the basis of coronary arteriograms the exercise and lactate tests proved to be reasonably sensitive (66 6 per cent) and specific (56 3 per cent and 68 8 per cent) in men In women the sensitivity was high (80 per cent) but the specificity low (exercise 35 per cent pacing 14 3 per cent and lactates 38 5 per cent, respectively) The pacing ECG was also highly unspecific in men (37 5 per cent) Seven patients gave totally normal findings The examination did not identify any specific group of patients with changes as indicatives of a constitutional disease of the myocardium The coronary changes indicated that even in this age it is proper to obtain arteriograms in patients with low working capacity even in the absence of any other changes that angina pectoris itself There are more false positive findings in women than in men in exercise tests and in many situations arteriography assures the best basis for further measures

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Effect of verapamil on normal sinoatrial node function and on sick sinus syndrome*

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Verapamil, a derivative of papaverine was originally introduced as an antianginal drug[1] It was subsequently found to have potent antiarrhythmic properties, in both experimental and clinical studies[3, 4] The drug is now commonly used for treatment of reentrant atrial tachyarrhythmias, for controlling ventricular rate in atrial flutter and fibrillation, and also for tachyarrhythmias associated with preexcitation syndrome[3, 5, 6] Current reports on its mode of action have focused attention on the effect of this drug on sinoatrial (SAN) and atrioventricular (AVN) nodes[7, 8] Previously, clinical studies demonstrated that a variety of supraventricular bradyarrhythmias, such as S A block atrial arrest and advanced A V block[9, 12] have been associated with administration of intravenous bolus of the drug Since the underlying cause of some atrial tachyarrhythmias is a damaged S A node,[13, 18] the use of verapamil in patients with sick sinus syndrome may be potentially dangerous Unfortunately, clinical information on the effects of this drug on human SAN function is inadequate[19, 20] to establish safe therapeutic patterns

The purpose of the present communication is to study the effect on SAN function of several concentrations of intravenous verapamil administered in the usual clinical range measured by determination of SAN recovery time and of corrected SAN recovery time after overdrive atrial pacing[7, 1, 21, 23] Patients with normal SAN function and with sick sinus syndrome (SSS) were studied beta receptor active drugs and parasympatholytic drugs were also administered to elucidate a possible mode of action in these circumstances

Material and methods

Sixty seven patients underwent hemodynamic and electrophysiologic studies (right and left sided catheterization, pressures LV cineangiogram coronary angiogram and atrial stimulation) and were divided into three groups Groups I and II included 15 patients with angina like chest pain 16 patients with asymptomatic sustained sinus bradycardia over 50 per minute 12 patients with arterial hypertension, and seven patients who underwent miscellaneous angiographic studies Their age range was from 21 to 83 years None of the patients were receiving antiarrhythmic agents digitalis or diuretics Group I patients were treated with verapamil alone in various concentrations to determine its effects on SAN function

Group II patients received beta receptor and parasympatholytic drugs in conjunction with verapamil

The Group III patients were previously diagnosed as having sick sinus syndrome (SSS) established by clinical findings, routine electrocardiograms Holter monitoring[13, 16, 1, 24, 25] and abnormal SAN suppression tests[13, 15, 21, 22] The age range was from 28 to 65 years and included four

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Supported by a grant from the Consejo de Desarrollo Cientifico y Humanistico de la Universidad de Los Andes (C D C H U L A)

Received for publication Jan 16 1978

Accepted for publication Apr 4 1978

Reprint requests Dr Abdel Fuenmayor Centro Cardiovascular Universidad de Los Andes, Mérida Venezuela

Presented in part at the Seventh World Congress of Cardiology Buenos Aires Argentina September 1974

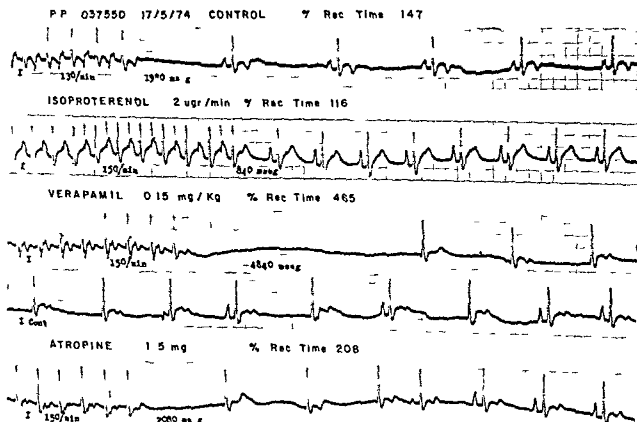


Fig 1 Lead II tracings recorded at double standardization from a patient with sick sinus syndrome Control post pacing pause of almost two seconds and a warming up phenomenon are observed *(upper strip)* Isoproterenol administration normalizes SAN recovery time *(second strip)* but verapamil administered intravenously doubles it allowing a junctional escape rhythm to appear *(third strip)* Sinus rhythm resumes 17 seconds after stopping artificial atrial pacemaking *(fourth strip)* Atropine did not revert completely the SAN depressing effect of verapamil in this patient *(lower strip)*

females and three males Four of these patients had angiographically proven coronary artery disease two had chronic Chagasic heart disease and one had no defined etiology Informed consent was obtained on all patients

Routine hemodynamic and angiographic studies were carried out as planned in all patients Thereafter (in 31 patients) a No 5F bipolar electrocatheter (Medtronic 6700) was passed via the right femoral vein and placed in a stable position in the high right atrium In 36 patients a No 6F tetrapolar electrocatheter (USCI) was used This catheter has two distal electrodes positioned for pacing and two proximal electrodes positioned in the proximities of the S A node for intraatrial electrogram recordings Tracings were obtained on a calibrated Hewlett Packard electrocardiograph or on a Mingograph (EM 81 Elema Schoenander) After positioning of the catheters a period of 30 minutes was allowed for stabilization before starting drug studies

SAN function was measured by performing overdrive atrial pacing with a 5880 A Medtronic external generator according to standard techniques [2] at paced frequencies of 90 110 130 150 and 180 per minute Extent of SAN suppression after pacing is proportional to the duration of post pacing pause measured from the last pacing artefact to the first spontaneous P wave Results were expressed as a percentage of control rate [2]

$$\text{Percent SAN recovery time (\% SAN rec time)} = \frac{\text{Maximal postpacing atrial pause (msec)} \times 100}{\text{Control P P interval}}$$

Corrected SAN recovery time (CSNRT) defined as the recovery interval in excess of the sinus cycle was also calculated [2] Sequences without

Table I Effect of verapamil on normal SAN function

	RR (msec)	*Max rec time (msec)*	*% SAN rec time*	*CSNRT (msec)*	*PR (msec)*	*% A V cond*
Control (n = 7)	751 ± 41	1017 ± 42	136 ± 4	263 ± 27	180 ± 6	9ı ± 3
0 10 mg /Kg 5 min post V	780 ± 61	1040 ± 63	135 ± 5	260 ± 36	210 ± 40	76 ± 9
Δ%	4 ± 5	4 ± 4	2 ± 6	4 ± 5	16 ± 8*	–37 ± 15
0 10 mg /Kg 15 min post V	728 ± 27	1020 ± 50	140 ± 4	293 ± 30	200 ± 30	ı0 ± 7
Δ%	–1 ± 2	1 ± 4	2 ± 2	7 ± 8	17 ± 8	–³5 ± 10
0 10 mg /Kg 30 min post V	737 ± 25	1057 ± 61	143 ± 4	320 ± 39	200 ± 14	72 ± 9
Δ%	2 ± 4	5 ± 13	6 ± 5	20 ± 15	14 ± 8	–22 ± 10
Control (n = 14)	883 ± 50	1134 ± 65	129 ± 3	251 ± 27	180 ± 7	96 ± 2
0 15 mg /Kg 5 min post V	799 ± 37	1157 ± 57	144 ± 4	357 ± 37	210 ± 2	61 ± 7
Δ7	–8 ± 3*	3 ± 7	16 ± 3	52 ± 16*	16 ± 3*	–36 ± 7*
0 15 mg /Kg 15 min post V	921 ± 53	1414 ± 145	156 ± 16	494 ± 131	210 ± 30	50 ± 10
Δ%	–3 ± 7	15 ± 14	26 ± 15*	90 ± 56	16 ± 5	–43 ± 10
0 15 mg /Kg 30 min post V	884 ± 67	1348 ± 135	152 ± 11	464 ± 100	210 ± 14	55 ± 13
Δ%	–2 ± 8	18 ± 12	20 ± 8	71 ± 42*	17 ± 5	–3ᴊ ± 13
Control (n = 9)	986 ± 54	1270 ± 80	128 ± 2	285 ± 30	190 ± 1	98 ± 2
0 20 mg /Kg 5 min post V	834 ± 48	1310 ± 107	155 ± 4	473 ± 59	230 ± 13	47 ± 8
Δ%	–14 ± 5**	3 ± 8	27 ± 4***	73 ± 20	19 ± 4***	–51 ± 8 **
0 20 mg /Kg 15 min post V	938 ± 51	1762 ± 265	186 ± 21	828 ± 225	230 ± 13	46 ± 8
Δ%	–5 ± 6	32 ± 17	57 ± 20	177 ± 68*	19 ± 4**	–50 ± 8
0 20 mg /Kg 30 min post V	967 ± 61	1537 ± 149	157 ± 8	570 ± ⁹0	230 ± 40	48 ± 6
Δ%	–5 ± 6	17 ± 15	27 ± 8	83 ± 30**	–20 ± 6*	–51 ± 6 *

= p < 0 05
= p < 0 005
= p < 0 0005
All results expressed as mean ± SEM
Abbreviations Max rec time = maximal post pacing pause % SAN rec time = per cent SAN recovery time CSNRT = corrected sinus node recovery time % AV cond = per cent AV conduction efficiency Δ% = per cent change as compared to control V = Verapamil

clear cut sinus escape beats after pacing were discarded and were repeated Longest maximal post pacing pauses, usually observed after pacing between 130 and 180/minute were used for comparison of results An approximate estima tion of A V conduction efficiency, expressed as per cent A V conduction was obtained by dividing ventricular rate by paced atrial rate at 130/minute This relationship is essentially a numerical expression of the Wenckebach phe nomenon and was calculated in our experiments (together with PR changes) as a secondary objec tive, to obtain an approximate idea of the effect of the drugs used on A V conduction

After a control value for SAN function was determined in all patients they were divided (as described previously) into three groups Thirty patients (Group I) with no evidence of SAN dysfunction were given commercially available intravenous verapamil (Manidon Knoll A G) in single bolus to establish the effect of several concentrations of this drug on normal SAN func tion, seven patients were administered verapamil at 0 10 mg /Kg 14 patients at 0 15 mg /Kg and nine patients at 0 20 mg /Kg Atrial overdrive pacing was repeated and SAN function measured at five, 15 and 30 minutes after the administra tion of the drug

The next 30 patients with normal SAN func tion (Group II) were further subdivided in an effort to demonstrate by what means verapamil exerts its effect on this pacemaker In six patients of Group II, the possibility of a beta blocking effect of verapamil was explored For this purpose isoproterenol (Isuprel Wintrop, 3 μgr/ minute) was administered for five minutes until heart rate response was stable Then the infusion was stopped and an additional five to ten minute period was allowed for hemodynamic changes to return to control levels At this time, an 0 20 mg /Kg bolus of verapamil was administered Seven minutes later isoproterenol infusion was started again at 3 μgr/minute and maintained for 10 minutes SAN function was measured immedi ately before, and five minutes after, the adminis tration of the drugs In the next six patients of

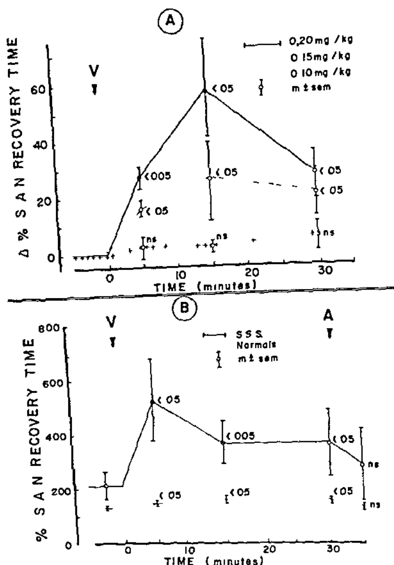


Fig 2 Effect of verapamil on SAN function in normal subjects *(panel A)* and in patients with sick sinus syndrome *(panel B)* *In panel A* the effects of three different doses of verapamil *(V)* are depicted Per cent changes in SAN recovery time as compared to control are represented *in ordinates* These effects are already significant at 5 minutes with doses of 0 15 and 0 20 mg /Kg of the drug reaching a maximum at 15 minutes after injection and lasting for more than 30 minutes *In panel B* the effect of a similar dose of verapamil (V = 0 15 mg /Kg) and of atropine (A = 0 0 5 mg /Kg) on patients with sick sinus syndrome and on subjects with normal function are compared Prolongation of per cent recovery time in SSS patients is fourfold that seen in patients with normal SAN function being maximal at 5 minutes and lasting for more than 30 minutes Atropine injected at this time returned per cent SAN recovery time to pre verapamil levels in both groups

Group II blocking of the beta cardiac receptor was achieved before administration of verapamil in an effort to determine if this blocking would alter the action of verapamil on SAN function consequently propranolol (Inderal ICI 0 1 mg / Kg) was given in 100 c c of 5 per cent C W solution over a 10 minute period SAN function determinations were made five and ten minutes after the end of the intravenous solution and immediately thereafter verapamil (0 20 mg /Kg) was administered intravenously Overdrive atrial pacing was repeated at five 15 and 30 minutes after the administration of verapamil In the remaining 18 patients of group II effects of blocking cholinergic receptors with 0 025 mg /Kg of atropine intravenously administered before

Table II Effects of isoproterenol and propranolol on verapamil induced changes in normal SAN function

	RR (msec)	*Max rec time (msec)*	*% SAN rec time*	*CSNRT (msec)*	*PR (msec)*	*% AV cond*
Control (n = 8)	941 ± 89	1254 ± 88	136 ± 5	313 ± 35	190 ± 9	9[illegible] ± 8
5 min post Isoproterenol	576 ± 33	808 ± 64	140 ± 5	232 ± 37	140 ± 4	100 ± 0
Δ%	−26 ± 6*	−29 ± 5	4 ± 2	−31 ± 7*	−23 ± 6	13 ± 10
5 min post Verapamil	929 ± 87	1525 ± 206	162 ± 8	609 ± 145	230 ± 20	48 ± 9
Δ%	−1 ± 7	20 ± 9*	22 ± 6**	95 ± 33*	22 ± 7	−44 ± 9
5 min post Isoproterenol	773 ± 55	993 ± 81	129 ± 4	220 ± 38	170 ± 10	90 ± 8
Δ%	−15 ± 7	−21 ± 8	−7 ± 4	−24 ± 12	−11 ± 5	−2 ± 9
Control (n = 6)	948 ± 117	1266 ± 130	135 ± 5	316 ± 36	180 ± 8	93 ± 6
5 min post Propranolol	1060 ± 106	1472 ± 154	139 ± 5	404 ± 66	190 ± 10	64 ± 10
Δ%	13 ± 5*	13 ± 2**	4 ± 5	29 ± 13	9 ± 4	−[illegible]8 ± 1[illegible]
10 min post Propranolol	1080 ± 125	1436 ± 154	144 ± 2	440 ± 46	190 ± 10	6[illegible] ± 3[illegible]
Δ%	17 ± 4*	13 ± 2**	9 ± 5	49 ± 21*	9 ± 4*	−27 ± 16
5 min post Verapamil	1028 ± 75	1996 ± 329	195 ± 31	1064 ± 404	240 ± 40	34 ± 7
Δ%	11 ± 6	80 ± 33	60 ± 30	225 ± 103*	35 ± 5	−60 ± 1[illegible]
15 min post Verapamil	1020 ± 102	2292 ± 517	224 ± 49	1272 ± 477	230 ± 8	3[illegible] ± 5
Δ%	9 ± 4	78 ± 36	89 ± 40*	275 ± 116	30 ± 6	−61 ± 10
30 min post Verapamil	1020 ± 63	1932 ± 350	190 ± 36	912 ± 338	220 ± 8	3[illegible] ± 5
Δ%	11 ± 7	55 ± 30	55 ± 34	177 ± 86	28 ± 6	−61 ± 10 *

= p < 0 05
= p < 005
= p < 0 000[illegible]
Isoproterenol = IV infusion 3 μgr/min Verapamil = IV bolus 0 20 mg /Kg Propranolol = IV infusion 0 1 mg /Kg Other abbreviations a in Table I

verapamil in seven patients and after 0 20 mg / Kg verapamil in eleven patients were studied to test possible vagal like action of the drug SAN function was measured immediately before and five to ten minutes after administration of the drugs

The methodology followed for Group III (seven patients with SSS) was as follows control levels of SAN function were determined 0 15 mg /Kg of verapamil were administered intravenously and SAN function redetermined at 5, 15, and 30 minutes post drug injection Finally, atropine (0 025 mg /Kg bolus) was given 35 minutes after verapamil administration followed five minutes later by SAN function measurements (Fig 1)

Changes observed in all parameters are expressed as per cent increase or decrease from control conditions (Δ%) Normal results in our laboratory for per cent SAN recovery time is 135 ± 22 (mean ±2 standard deviations) and for CSNRT is 289 ± 176 msec These results are in agreement with those currently reported[11 13 21 2] Standard techniques (paired Student t test correlation coefficient determinations and lineal correlation analysis) were applied in order to assess statistical significance of data calculated in a pre programmed 9810 Hewlett Packard desk computer

Results

1 Effect of verapamil on normal SAN function (Group I) Results are summarized in Table I and in Fig 2A Patients given 0 10 mg /Kg verapamil did not show significant changes in heart rate % SAN rec time or CSNRT evidencing no measurable effect on SAN function Definitive prolongation of PR interval (14 to 17 per cent p < 0 05) and a decrease in AV conduction efficiency (−37 per cent p < 0 05) were observed the effect being maximal at 5 minutes and lasting for more than 30 minutes These changes suggest an important depressant effect on AV node function

When the drug dose was raised to 0 15 mg /Kg a small but significant shortening of RR interval was observed (−8 per cent p < 0 05) five minutes post drug administration Significant prolongation of % SAN rec time was observed at 5 minutes reaching a maximum of 26 per cent at 15 minutes (p < 0 05) and lasting for more than 30 minutes Similar changes were also noticed in CSNRT values (maximal increase of 96 per cent at 15 minutes p < 0 05) demonstrating an early

Table III Effects of atropine on verapamil induced changes in normal SAN function

	RR (msec)	Max rec time (msec)	% SAN rec time	CSNRT (msec)	PR (msec)	% AV cond
Control (n = 7)	8[illegible] ± 46	1066 ± 67	129 ± 2	243 ± [illegible]6	0.18 ± 0.02	96 ± 4
5 min post Atropine	591 ± 39	709 ± 59	119 ± [illegible]	114 ± 20	0.16 ± 0.0[illegible]	100 ± 0
Δ%	−28 ± 4	−35 ± 9	−10 ± 2 *	−54 ± 4	−13 ± 2	4 ± 3
10 min post Verapamil†	606 ± 51	857 ± 97	140 ± 6	251 ± 51	0.16 ± 0.01	85 ± 7
Δ%	2 ± 3	20 ± 6	[illegible]0 ± 5	129 ± 28	13 ± 4	−15 ± 7
Control (n = 11)	1010 ± 55	1315 ± 58	131 ± 3	304 ± 24	0.19 ± 0.02	90 ± 5
5 min post Verapamil	915 ± 49	1340 ± 67	150 ± 5	452 ± 40	0.22 ± 0.02	51 ± 6
Δ%	−8 ± 3	2 ± 4	[illegible]0 ± 4	46 ± 1[illegible]	21 ± 4	−43 ± 6
5 min post Atropine	71[illegible] ± 44	960 ± 78	134 ± 4	251 ± 38	0.18 ± 0.0[illegible]	88 ± 2
Δ%	−28 ± 4	−28 ± 4	3 ± 6	−12 ± 17	−5 ± 3	1[illegible] ± 6

* = $p < 0.05$
** = $p < 0.005$
*** = $p < 0.0005$
Atropine = IV bolus 0.0.5 mg/Kg
Verapamil = IV bolus 0.20 mg/Kg
†Results obtained after administration of verapamil are compared to those seen after administration of atropine and not to control results.
Other abbreviations as in Table I

and sustained depressant effect on normal SAN function PR interval prolongation and the decrement in AV conduction were little more pronounced at this dose level At a dose of 0.20 mg/Kg the RR interval shortened to −14 per cent ($p < 0.05$) 5 minutes after injection but no significant changes were observed later Changes in % SAN rec time were even more pronounced prolonging to 27 per cent at 5 minutes ($p < 0.05$) 57 per cent at 15 minutes and 27 per cent at 30 minutes post drug administration (both changes $p < 0.05$) CSNRT changes paralleled those observed in per cent SAN rec time reaching a maximum of 177 per cent at 15 minutes ($p < 0.05$) In contrast AV conduction efficiency decreased little more than with previous dose levels and the increase in PR interval was also similar These changes seemed to be uniform throughout 30 minutes of observation after the drug was given

These results indicate that verapamil exerts an important dose related depressant effect on normal SAN function The effect is already discernible 5 minutes post drug administration is maximal at 15 minutes and still significant 30 minutes post injection Effect of verapamil on the AV node seems to be present at a lower dosage and is maintained uniformly for 30 minutes after administration of the drug but it may be less dose dependent than the effect on SAN function In addition to these observations there was noted an increased frequency of atrial arrhythmias such as SA block and atrial standstill accompanied always by junctional or ventricular escapes Advanced AV block was also observed in two patients given 0.20 mg/Kg it lasted for more than 5 minutes necessitating the use of temporary artificial pacemaking

2 Effect of isoproterenol propranolol and atropine on verapamil induced changes on normal SAN function (Group II) Results are summarized in Tables II and III and in Figs 3 and 4 Isoproterenol infusion maintained at a rate of 3 μgr/minute over a 5 minute period caused a typical beta receptor stimulant effect that is shortening of RR interval PR interval and CSNRT It did not alter % SAN REC time or per cent AV conduction Once this drug was withdrawn and control condition reestablished verapamil (0.20 mg/Kg) was administered Changes observed were similar to those previously described at 5 minutes post injection increase in % SAN rec time and in CSNRT lengthening of PR interval and a decrease in AV conduction efficiency When isoproterenol infusion was restarted a complete return to control conditions was obtained for % SAN rec time and per cent AV conduction RR interval CSNRT and PR interval showed shortening similar to that observed when isoproterenol was administered before verapamil This response indicates that verapamil did not block cardiac beta receptors at this dosage (Fig 3A)

In six patients administration of intravenous

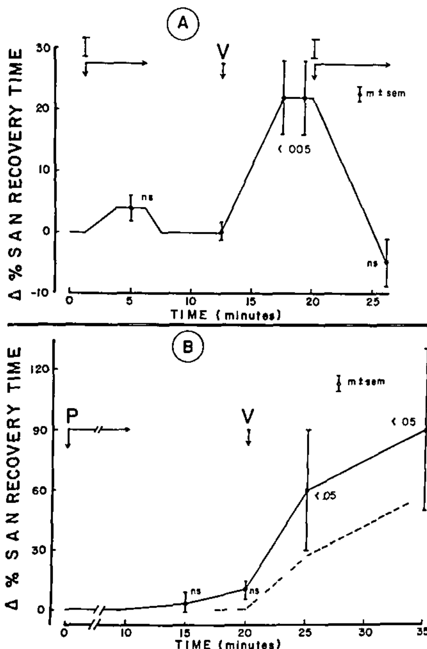


Fig 3 Effect of beta receptor active drugs on verapamil induced changes in normal SAN function *Panel A* Administration of isoproterenol infusion (I = 3 μgr/minute) does not modify significantly SAN recovery time Verapamil injection (V = 0 20 mg /Kg) prolongs it after 5 minutes but it does not prevent normal response to reinfusion of isoproterenol at same previous dosage *Panel B* Infusion of propranolol (P = 0 1 mg /Kg) does not prolong significantly SAN recovery time Effects of verapamil (V = 0 20 mg /Kg) administered 10 minutes after stopping propranolol infusion are more than double those expected for this dose suggesting a synergistic depressant effect of these two drugs on SAN function *Dotted line at the right of the graph* represents mean results obtained with a dose of 0 20 mg /Kg of verapamil in normal subjects without blocking of beta receptors This is the same curve represented in *Fig 2* redrawn here for purposes of comparison of results

propranolol (0 1 mg /Kg) caused significant prolongation of RR interval at 5 minutes (13 per cent) and at 10 minutes (17 per cent) It also prolonged CSNRT (29 per cent at 5 minutes 49 per cent at 10 minutes, $p < 005$) PR interval (9 per cent) and per cent AV conduction (27 per cent) without modifying % SAN rec time Five minutes after the administration of 0 20 mg /Kg verapamil to those patients already given propra nolol the prolongation of % SAN rec time (60 per cent $p < 0 05$) and of CSNRT (225 per cent $p < 005$) was twofold and threefold that observed after the administration of verapamil alone This enhancement of verapamil effect was also observed on AV nodal function PR prolonged to 35 per cent and AV conduction efficiency decreased to −49 per cent ($p < 0005$) These changes increased to a maximum at 15 minutes post verapamil administration but only effects on AVN function persisted significantly up

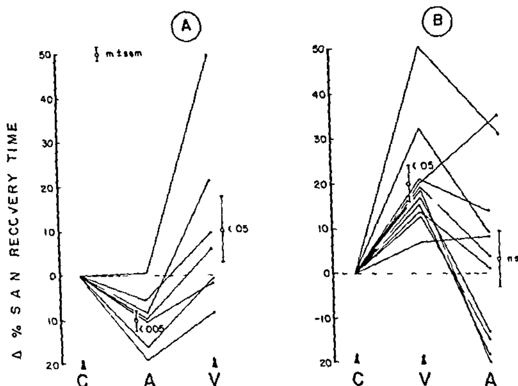


Fig 4 Effect of atropine on verapamil induced changes in normal SAN function *Panel A* atropine (A = 0 0?5 mg /Kg) administered ten minutes after injecting intravenous verapamil (V = 0.20 mg /Kg) shortens SAN recovery time at 5 minutes post injection Prolongation of this parameter is observed in all patients five minutes after administration of verapamil. *Panel B* Administration of same dose of verapamil (V = 0.20 mg /Kg) causes expected prolongation of SAN recovery time at 5 minutes in all patients Atropine (A = 0 0?5 mg /Kg) administered seven minutes after injection of verapamil shortens SAN recovery time in only four out of 11 patients. Results are expressed as per cent changes from Control *(C) SAN recovery time in the ordinates* in both graphs

to 30 minutes (Table II) This suggests that verapamil and propranolol have a synergistic effect on SAN and AV function which lasts up to 15 minutes for SAN and for more than 30 minutes for AVN function (Fig 3B) However verapamil induced shortening of RR interval was not observed after blocking of the beta receptors it would seem then that this effect of verapamil must be brough about by a mechanism other than that which explains the action of the drug on SAN function In the seven patients with normal SAN function given atropine prior to verapamil (Table II Fig 4A) there was an initial shortening of RR and PR intervals (−28 per cent and −13 per cent $p < 0 01$) per cent SAN rec time and CSNRT also decreased (−10 per cent and −54 per cent $p < 001$) When 0 20 mg /Kg of verapamil was administered in these circumstances a definite prolongation of CSNRT and increase of per cent SAN rec time were observed (129 per cent and 20 per cent $p < 005$) along with prolongation of PR interval (13 per cent) and decrease of AV conduction efficiency (−15 per cent) Eleven patients of this same Group II received verapamil followed by atropine in seven of these eleven patients (64 per cent) atropine failed to return to control values the prolongation of SAN rec time and of CSNRT caused by verapamil These results suggest that the action of verapamil is not exerted via stimulation of cholinergic cardiac receptors

3 Effect of verapamil on sick sinus syndrome (Group III) Patients with SSS (Table IV Fig 2B) showed a somewhat prolonged RR interval Mean % SAN rec time (212 ± 5) and CSNRT (1004 ± 359 msec) were significantly longer than normal AV conduction efficiency was slightly lower than normal (82 per cent) and PR interval was normal Administration of a single bolus of 0 15 mg /Kg verapamil did not affect RR interval % SAN rec time showed a threefold prolongation (305 per cent $p < 005$) and CSNRT a

Table IV Effects of verapamil on SAN function in patients with sick sinus syndrome

	RR (msec)	*Max rec time (msec)*	*% SAN rec time*	*CSNRT (msec)*	*PR (msec)*	*% AV cond*
Control (n = 7)	1029 ± 82	2033 ± 369	212 ± 51	1004 ± 359	160 ± 10	82 ± 9
5 min post Verapamil	1157 ± 143	5703 ± 1093	517 ± 149	4754 ± 1696	210 ± 20	46 ± 10
Δ%	18 ± 21	218 ± 61 *	305 ± 106	418 ± 118*	27 ± 7 *	−40 ± 19
15 min post Verapamil	1203 ± 138	4793 ± 1760	359 ± 84	3633 ± 1663	200 ± 20	44 ± 10
Δ%	19 ± 20	164 ± 43*	160 ± 43* *	354 ± 118**	24 ± 7**	−45 ± 14
30 min post Verapamil	1131 ± 127	4283 ± 1823	355 ± 119	2960 ± 1520	210 ± 20	61 ± 10
Δ%	16 ± 20	78 ± 40*	143 ± 72*	181 ± 83*	27 ± 7**	−21 ± 9
5 min post Atropine	940 ± 111	3223 ± 1862	282 ± 423	2283 ± 1768	160 ± 10	78 ± 11
Δ%	−3 ± 18	18 ± 40	60 ± 67	19 ± 41	0 ± 14	−4 ± 8

* = p < 0 05
** = p < 0 005
*** = p < 0 0005
Verapamil = 0 15 mg /Kg
Atropine = 0 025 mg /Kg
Other abreviations as in Table I

fourfold prolongation (418 per cent p < 005) at five minutes after verapamil In contrast, lengthening of PR interval and decrease in AVN conduction efficiency were of the same magnitude as those caused by the same drug dose in patients with normal SAN function This marked prolongation of % SAN rec time and of CSNRT decreased at 15 minutes post injection of verapamil but nevertheless persisted up to 30 minutes Changes in PR interval and AV conduction efficiency were maintained at the same level for 15 minutes and showed little decrease at 30 minutes post drug administration At this time administration of atropine induced normalization of SAN function parameters in two patients return to pre verapamil levels in one, and no response in the remaining four (two patients with Chagas disease and two with coronary artery disease) On the whole atropine returned % SAN rec time and CSNRT to pre verapamil values as it did all changes in PR interval and AV conduction efficiency (Table IV and Fig 2B) After administration of verapamil the appearance or worsening of the degree of SA block even with progression to atrial arrest and of prolonged periods of asystole needing artificial temporary pacemaking after overdrive atrial pacing were frequently observed (Fig 1) The four patients who did not respond to atropine needed temporary pacemakers left in place until definitive pacemaker implantation was undertaken

These results indicate that the patients with SSS are at least four or five times more sensitive to verapamil than subjects with normal SAN function The effect is maximum at approximately five minutes and persists up to 30 minutes, frequently it is not reversed at all by atropine administration thus necessitating temporary artificial pacing Depressant effect on AVN function seems to be of the same magnitude as that observed in subjects with normal SAN function

Discussion

The use of overdrive atrial pacing for determining sinus node recovery time represents a useful tool for measuring over all SAN function, it is reproducible, involves few complications and is easily applied to clinical studies [15, 21, 2, 6] Prolongation of CSNRT has been demonstrated in instances of SAN injury,[26] in cases of sick sinus syndrome,[15, 1, 2] and following vagal stimulation [28] In addition, the influence of atropine [15, 1] isoproterenol [6] and beta receptor blocking drugs on CSNRT has been described [26] but little data has been gathered regarding effects of other drugs such as verapamil [19] Our studies clearly demonstrated the depressant effect that verapamil exerts on normal SAN function This is manifested by a dose related prolongation of SAN recovery time after overdrive atrial pacing a prolongation that appears early and lasts up to 30 minutes in duration Similar animal experimental results have been reported elsewhere [17, 22] In studies using selective perfusion of SAN and AVN areas, SAN function exhibited a greater sensitivity to verapamil than AVN function [22]

We frequently observed SA block and atrial arrest accompanying prolongation of SAN rec time after administration of the drug but it should be noted that the first effect on the heart was a significant decrease in AV conduction efficiency (Table I Fig 2A) even at doses which seem not to affect SAN function [9] Intra atrial conduction atrial tissue and ventricular tissue properties are little or not at all affected by the drug [1 1 0] A consensus exists that the decrease in AV conduction efficiency is the main and most useful electrophysiologic effect of verapamil and explains its efficacy in reversing arrhythmias which involve circus movement or AVN reentries In these circumstances the previously demonstrated SAN depressing effect must be con idered an undesirable effect on the drug since it is a frequent cause of complications observed in clinical trials [9]

The effects of verapamil on SAN function are not mediated via blocking of cardiac beta sympathetic receptor [2] Its administration did not affect the response of SAN to isoproterenol in ours (Table II Fig 3A) and other experiments [6] Recent studies have elucidated that the negative inotropic action and antiarrhythmic properties are best explained by its interference with the slow inward calcium current observed in phase 2 and 3 of the action potential [2 3] or on the slow channels itself Generation of normal action potentials in SAN and AVN may depend mainly on the slow ionic current carried by Ca Na or both and so these nodes are more sensitive than the rest of cardiac tissue to calcium antagonists such as verapamil This would explain the rather selective and singular depressant effects of this drug on SAN automaticity and on AVN conduction Importantly enough reversion of all effects of verapamil on SAN and AVN by isoproterenol may be explained by the property this drug has of enhancing slow inward current

Beta adrenergic receptor blockers exert their antiarrhythmic action preventing catecholamines from acting on excitable cells Also they may interact within the cell membrane to limit its permeability to calcium ions [26] The additive and marked depressant effects on SAN and AVN function observed in patients given verapamil after blocking with propranolol (Table II Fig 3B) can then be explained on the basis of a double interference with calcium entry to the cell exerted by both drugs The increased frequency of complications related to the simultaneous clinical use of these two drugs[3] can be explained similarly

Action of verapamil on SAN function was not blocked by previous administration of atropine nor did this drug reverse to normal verapamil induced prolongation of SAN rec time in most of our normal subjects (Table III Fig 4) Similar results were reported in several other studies [6 1 3 27 4 5] with few exceptions [2] and they seem to confirm that verapamil acts directly on SAN cell rather than indirectly through stimulation of cholinergic receptors A possible explanation for atropine induced shortening of SAN rec time in some of our cases is that this drug inhibits the usually more preponderant influence of parasympathetic tone[3] [8] on SAN activity or that it improves conduction from SA node pacing cells to the atrium thereby facilitating recovery after overdrive atrial pacing [37]

The slight increase in heart rate observed at 5 minutes post verapamil administration at doses of 0 15 and 0 20 mg /Kg has also been observed in previous reports [19 2 3 3] Its short duration and the fact that it is not observed in cases of previous beta receptor blocking nor in cases with SSS nor in experimental selective perfusion to SAN area [4] suggests that it may be due to reflex sympathetic stimulation secondary to a brief decrease in peripheral resistance and in blood pressure [2 8 31] However some authors reported these changes in heart rate without a concomitant decrease in peripheral resistance [31] but as we did not measure hemodynamic changes post verapamil we cannot draw any conclusion on this matter

In our study patients with SSS displayed a variety of atrial tachyarrhythmias [1 1] susceptible to treatment with verapamil [2 2] Only those patients were chosen who also showed abnormal response to overdrive atrial pacing [1 2 21] in order to be confident as to the degree of SAN dysfunction for each of them The presence of Wenckebach phenomenon at atrial paced rates of 130/minute was also more frequent among them evidencing some degree of concomitant AV nodal disease as well [1] As could be expected given the already altered SAN function [5 9] effects of verapamil are much more marked and severe on SAN function of these patients but effects on AVN function are no different from those caused

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	RR (msec)	Max rec time (msec)	% SAN rec time	CSNRT (msec)	PR (msec)	% AV cond
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by the drug in patients with normal SAN and AVN function However, this depression of AVN function acquires a different functional meaning in patients with SSS, since they depend fundamentally on presumed escape rhythms originating mainly from this AVN area Verapamil then exerts a double deleterious effect on SSS patients, depressing even more the damaged SAN function and potentially suppressing possible and vital escape rhythms coming from the AVN area

In four of seven patients, atropine administered intravenously when the effect of verapamil was fading away failed to reverse the depressant action on SAN function although it normalized AV conduction in all cases In the two cases of chronic Chagasic cardiomyopathy this unresponsiveness might be attributed to cardiac parasympathetic innervation damage [41] or in all four cases to intrinsic refractoriness inherent to organic SAN damage,[7,15,1,2] or to a more marked direct effect exerted by verapamil on these damaged SA nodes Evidence supporting the last point in particular is currently lacking Partial unresponsiveness to atropine in cases of SSS may be explained by postulating that the sick sinus shows hyperresponsiveness to acetylcholine released by overdrive atrial pacing,[15,1] and atropine administered at the usual dose level was not able to reverse all its effects [40] Overdrive stimulation and consequent release of acetylcholine can also increase in severity preexisting conduction blocking within the SAN [33] Verapamil could cause a similar increase and simultaneously depress automaticity of SAN pacing cells Atropine then may act only on effects of acetylcholine released, thus partially improving the recovery time Acetylcholine causes an increase in cell membrane permeability to K [33] which can be blocked by atropine whereas it cannot inhibit the Ca changes provoked by verapamil In normal cells, these opposite ionic effects of verapamil and atropine may counterbalance each other In cases of SSS, however this balance may be upset by the presence of organic SA damage, intranodal block and other as yet undetermined influences, and the persistence of verapamil induced depression of SAN function is therefore favored

Summary

Sixty patients, normal with respect to SAN function screened to exclude cardiomyopathy, and seven patients with sick sinus syndrome underwent overdrive right atrial pacing at progressively increasing rates before and after administration of different doses of verapamil Sinoatrial node corrected recovery time and per cent recovery time related to control PP were determined before and five, 15, and 30 minutes after the administration of the drug Moderate prolongations of these parameters lasting for more than 30 minutes were observed with doses of 0 15 and 0 20 mg /Kg of verapamil, evidencing a depressant effect on normal SAN function, concomitant and earlier AV conduction impairment was also observed These changes were dose related and were eliminated by administration of isoproterenol, but not by atropine intravenously Action of the drug is probably exerted directly on SAN and AVN cells since it did not show any significant effect on beta sympathetic receptors or on cholinergic receptors

In patients with sick sinus syndrome, effect of verapamil on SAN function is four or five times more intense, with concomitant impairment of AVN function, several of these patients had prolonged asystoles after administration of the drug which did not reverse with atropine injection It is concluded that the marked depression of SAN function caused by verapamil in patients with sick sinus syndrome contraindicates its use for treatment of any of the atrial arrhythmias which form this syndrome Precautions must be taken also when treating any supraventricular arrhythmia on an emergency basis since they may be caused by an as yet undiagnosed sick sinus syndrome

The authors wish to thank all medical and paramedical personnel of the Cardiovascular Center for their cooperation in this study and Mrs Raquel Kowalsky and Mrs Francesca Giegengack for their secretarial work

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under the artery but the vessel was not occluded Coronary occlusion was verified by the appearance of S-T segment elevation in the epicardial electrogram obtained from the ischemic region and by cyanosis and systolic bulging of the ventricular wall distal to the ligature The unipolar epicardial electrode consisted to a 1 cm diameter felt pad sutured to the epicardium and attached to a medicine dropper containing saline and the electrode lead by a strip of ⅛ inch umbilical tape The epicardial electrode was referenced to the combined standard limb lead (Wilson central terminal) Ventricular arrhythmias were treated with 0 5 to 2 0 mg/Kg doses of intravenous lidocaine

Hemodynamic measurements Aortic and left ventricular pressures were measured using Statham P23Db pressure transducers connected to saline filled polyethylene (PE 260) catheters Pressure signals and the first derivative of left ventricular pressure dP/dt were displayed on a Physiograph recorder (Narco Bio Systems Houston Texas) together with either Lead II of the electrocardiogram or the epicardial electrogram Heart rate left ventricular end diastolic pressure left ventricular systolic pressure and maximum dP/dt were measured directly from the Physiograph records

Cardiac output was measured using the saline indicator dilution technique and the continuous flow conductivity cell described by Geddes and associates[7] The change in blood resistivity with the addition of sodium chloride ($\Delta\rho/\Delta C$) is a function of blood temperature and packed cell volume Thus the values of $\Delta\rho/\Delta C$ at 37 C and different packed cell volumes reported previously by Geddes and co workers[7] were corrected to blood temperature t using the expression

$$\frac{\Delta\rho}{\Delta C_{t}} = \frac{\Delta\rho}{\Delta C_{37C}} (1 + 0036 (37 - t))$$

Sodium heparin (1 0 mg/Kg) was given intravenously every 2 to 3 hours to prevent clot formation in the cell Cardiac index stroke index peripheral vascular resistance and left ventricular minute work were calculated by established methods

Induction of hypothermia Hypothermia was induced by covering the dogs with bags of flake ice and by circulating ice water through the coils of a rubber mat under the dogs Esophageal or blood (subclavian artery) temperature was continuously monitored using a thermistor (Yellow Springs Instrument Co Yellow Springs Ohio) When the core body temperature reached 27°C the ice was removed and the body temperature was allowed to equilibrate A body temperature near 26°C was maintained by bags of ice or warm overhead lights as needed



Fig 1 Representative photographs of mirror image ventricular slices taken from a dog heart after 5 hours of LAD coronary artery occlusion The anterior wall of the left ventricle *(LV)* is directed towards the center of the photographs *a* shows the opposing surfaces of the two slices after India ink perfusion The light areas of the cut surfaces are uninked (ischemic) *b* shows the same surfaces of the slices after incubation in NBT stain The light areas of the cut surfaces are unstained (injured)

Identification and quantitation of ischemic myocardium In dogs with coronary occlusions the region of myocardial ischemia was identified by perfusing a dilute India ink suspension through the patent coronary vascular bed Cardiac perfusion was accomplished by withdrawing the left ventricular pressure catheter to the aortic root (verified by pressure measurements) A ligature was placed around the right brachiocephalic artery containing the catheter The left subclavian artery the precava the post

Protection of ischemic myocardium by whole-body hypothermia after coronary artery occlusion in dogs

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The survival of myocardium distal to an occluded coronary artery depends on a delicate balance between oxygen supply and oxygen demand. Interventions which either reduce myocardial oxygen requirements or increase myocardial oxygen availability have been found to decrease ischemic injury.[1-3]

Whole-body and local hypothermia have been used extensively in patients during cardiopulmonary bypass surgery to lower myocardial oxygen demand and thereby minimize the ischemic injury resulting from temporary anoxia.[illegible] However, the value of lowering the body temperature to decrease ischemic injury after coronary occlusion is not clear. Several investigators have concluded that hypothermia is contraindicated in recent myocardial infarction because of a high incidence of ventricular fibrillation observed in dogs.[illegible] However, in all of these studies a coronary artery was ligated after the animal was hypothermic, when the heart is highly vulnerable to mechanical stimulation. Other studies in which coronary occlusion preceded hypothermia have shown that dogs not only tolerated moderate hypothermia (25 to 30°C.) without ventricular fibrillation but also demonstrated better hemodynamic recovery following rewarming than controls.[illegible] Ginks and colleagues[illegible] reported a significant reduction in ischemic injury after coronary occlusion in dogs using a combination of hypothermia, intra-aortic balloon counterpulsation, intravenous propranolol, and coronary reperfusion, but the simultaneous use of several interventions did not permit the evaluation of hypothermia alone. The objective of the present study was to determine if moderate hypothermia without rewarming reduces ischemic injury after coronary artery occlusion in the anesthetized open-chest dog.

Materials and methods

Animal preparation. Twenty-eight mongrel dogs of both sexes, weighing between 4 and 18 kilograms, served as subjects. Anesthesia was induced by intravenous pentobarbital sodium (35.5 ± 1.7 mg./Kg.) and was maintained at stage III, plane ii according to the criteria of Lumb[16] by additional doses (3.5 ± 0.3 mg./Kg.) given as needed. The chest was opened by median sternotomy and the heart was supported in a pericardial cradle formed by suturing the free edges of the incised pericardium to the chest wall. Ventilation was maintained through a cuffed endotracheal tube by an intermittent positive-pressure ventilator using room air. Blood pH, pCO_2, and pO_2 were monitored in several dogs to determine that ventilation was adequate. The exposed heart was frequently moistened with Ringer's solution containing sodium lactate to prevent desiccation.

In 23 dogs, the left anterior descending coronary artery was isolated above the first major diagonal branch and was occluded with a silk suture. In five control dogs, a suture was passed

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Received for publication Jan. ?0, 19 8.
Accepted for publication May 5, 1978.

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Dr. Abendschein was supported by a predoctoral fellowship from the American Heart Association, Indiana Affiliate, Inc.

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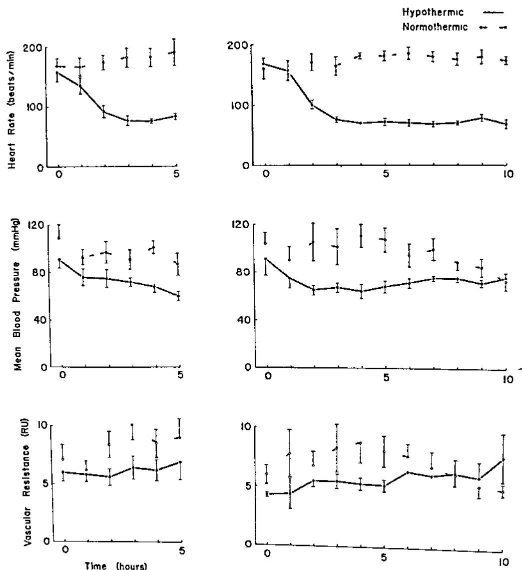


Fig 3 The effect of hypothermia on heart rate mean blood pressure and vascular resistance during periods of 5 and 10 hours of coronary artery occlusion Time 0 indicates occlusion *Points* represent the mean (n = 5) ± one standard deviation indicates that the mean values of the hypothermic and normothermic groups differ significantly (p < 0 05)

ylin and eosin and were examined for signs of early myocardial necrosis

Experimental design The left anterior de scending coronary artery was occluded in 23 dogs and sham occluded in five dogs Beginning 30 minutes later the body temperature of 12 dogs with coronary occlusions and all five sham operated control dogs was reduced to 26 C The body temperature of the remaining 11 dogs was maintained at 37 C Hemodynamic data were collected immediately before occlusion and at one hour intervals thereafter In sham operated dogs the intact hearts were perfused with Ringer s solution and the sliced ventricles were stained with NBT 5 hours after sham occlusion These dogs served to determine the incidence of myocar dial injury during hypothermia alone In dogs with coronary artery occlusions the intact hearts of surviving animals were perfused with Ringer s solution and India ink to define the region of ischemia after either 5 or 10 hours of coronary occlusion (five normothermic and five hypother

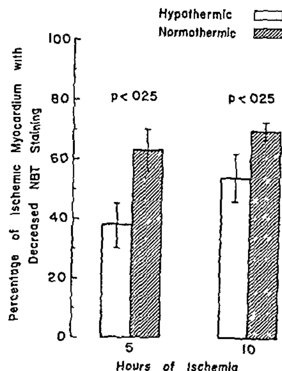


Fig 2 The effect of reducing body temperature to 26 C on the percentage of the ischemic myocardium with decreased dehydrogenase enzyme after either 5 or 10 hours of coronary artery occlusion *Bars* represent group means (n = 5) *Vertical lines* indicate one standard deviation

cava, and the aorta were ligated in succession Ringers solution containing sodium lactate (37°C) was first perfused through the coronary arteries *via* the aortic catheter at 120 to 150 mm Hg pressure to clear the heart of blood The atrial appendages were incised to permit drainage of fluid Perfusion with Ringers solution was stopped when the effluent from the atrial appendages cleared (about 200 ml of perfusate was required) Then a 10 per cent mixture by volume of India ink (Pelikan drawing ink, black No 17) in Ringers solution (37°C) was perfused at 120 to 150 mm Hg pressure until the posterior wall of the left ventricle was uniformly blackened (about 50 ml of ink perfusate was required) The hearts of dogs which did not receive coronary occlusions were perfused only with Ringers solution

The ventricles were sectioned into five 0 5 to 1 0 cm thick transverse slices The slices were weighed and photographs showing the mirror image surfaces were taken using Polaroid Continuous Tone (Type 46L) black and white transparency film A red filter was used to intensify the contrast between inked and noninked myocardium Enlarged (8 × 10) black and white prints (Kodak Velox F 2 photographic paper) similar to the one shown in Fig 1*a*, were cut and weighed to determine the ratio of unperfused to perfused area for each slice surface The average ratio of areas for both surfaces of a slice was multiplied by the tissue weight to determine the weight of ischemic myocardium in each slice

Macroscopic enzyme mapping of ischemic myocardium Nitrobluetetrazolium (NBT) staining was used to identify injured myocardium, since histologic indices of myocardial injury may not be reliably quantitated during the first 12 hours of coronary occlusion Viable cells containing active dehydrogenase enzymes reduce NBT forming a deep purple diformazan deposit In contrast, injured cells irreversibly lose dehydrogenase enzymes within 2 to 4 hours from the onset of ischemia and do not form the diformazan residue[18] The ventricular slices were incubated for 30 minutes at 37°C in a preheated solution consisting of 0 5 mg/ml of NBT (ICN Pharmaceuticals Inc Cleveland, Ohio) in 0 1 M phosphoric acid buffer (pH 7 4) without substrate

After incubation in NBT, the slices were rephotographed Enlarged black and white prints similar to the one shown in Fig 1*b*, were cut and weighed without knowledge of treatment group to determine the ratio of unstained to stained area for each slice surface Any area with less than maximum staining was considered injured The average ratio of both slice surfaces was used to calculate the weight of enzyme deficient myocardium in each slice In dogs with coronary occlusions, the percentage of ischemic myocardium having decreased NBT staining was determined for the whole heart Expression of the amount of injured (unstained) myocardium as a percentage of the ischemic (uninked) myocardium reduced the effect of inevitable variations in size and homogeneity of infarcts produced in dogs

Microscopic evaluation of injury In several dogs with coronary occlusions the ventricular slices were prepared for light microscopy to evaluate histopathology in areas of decreased NBT staining The slices were fixed in 10 per cent buffered neutral formalin immediately after the macroscopic analysis Following at least one week in formalin fixative blocks containing equal portions of NBT stained and unstained tissue were embedded in paraffin and cut at a thickness of 8 to 10 μ in a plane parallel to the NBT stained surface The sections were stained with hematox

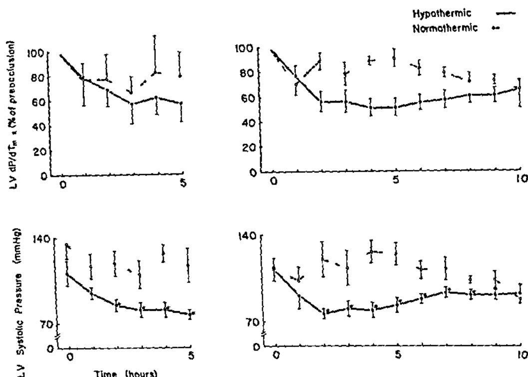


Fig 5 The effect of hypothermia on maximum left ventricular *(LV)* dP/dt and LV systolic pressure during periods of 5 and 10 hours of coronary artery occlusion Time O indi ates occlusion *Points* represent the mean (n = 5) ± on standard deviation The absolute values of dP/dt at time O" were 2 640 mm Hg/sec in the hypothermic group and 4 680 mm Hg/sec in the normothermic group of the 5 hour study ($p < 0\ 05$) and 3 120 mm Hg/sec in the hypothermic group and 3 160 mm Hg/sec in the normothermic group of the 10 hour study (p = N.S) * indicates that the mean values of the hypothermic and normothermic groups differ significantly ($p < 0\ 05$)

fibrillation was not significantly increased by hypothermia after coronary occlusion Of the 23 dogs that received coronary occlusions two hypothermic dogs and one normothermic dog developed ventricular fibrillation The data from these dogs have not been included in the following analysis The use of lidocaine to treat arrhythmias and delay of cooling until after the intense post occlusion arrhythmic period (i e 30 minutes) probably contributed to the low incidence of ventricular fibrillation in these studies

Size of the ischemic region The ischemic region produced by ligation of the left anterior descending coronary artery was clearly visible in transverse ventricular slices after perfusing the heart with India ink solution (Fig 1*a*) This region was located in the anterior wall of the left ventricle including the anterior papillary muscle and reaching the adjacent lateral and septal walls The average weight of ischemic myocardium was 13 Gm ranging from 6 to 30 Gm the average weight of the twenty dog hearts was 78 Gm ranging from 52 to 132 Gm The size of the ischemic region did not differ significantly between groups in this study ($p > 0\ 05$)

Myocardial injury in the ischemic region Following NBT staining portions of the ischemic region with decreased intracellular dehydrogenase enzyme were readily visible upon gross inspection of the tissue and were easily quantitated in black and white photographs of the ventricular slices (Fig 1*b*) Fig 2 shows the effect of moderate hypothermia on ischemic injury The percentage of the ischemic region which did not react with NBT was significantly lower in hypothermic dogs than in normothermic dogs after either 5 or 10 hours of coronary occlusion Five hours after coronary occlu ion the injured tissue appeared grossly as a patchy pale area in the ischemic subendocardium of the hypothermic dog hearts In contrast in the ischemic region of normothermic dog hearts the injured tissue appeared as a

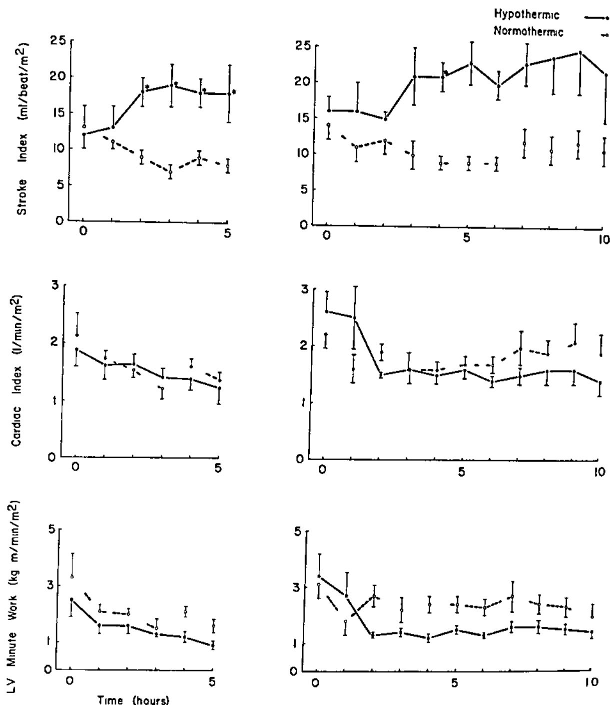


Fig 4 The effect of hypothermia on stroke index cardiac index and left ventricular *(LV)* minute work during periods of 5 and 10 hours of coronary artery occlusion Time O indicates occlusion *Points* represent the mean (n = 5) ± one standard deviation * indicates that the mean values of the hypothermic and normothermic groups differ significantly ($p < 0.05$)

mic dogs at each time period) The ischemic region was measured grossly in transverse slices of the ventricles, and the slices were stained with NBT to identify injured myocardium within the ischemic region The extent of myocardial injury was evaluated grossly and was expressed as a percentage of the ischemic region In eight hypothermic dogs and six normothermic dogs ventricular slices were prepared for histopathologic study Histochemical and hemodynamic measurements were analyzed by unpaired Student s t tests

Results

The hearts of sham operated dogs subjected to 4½ hours of hypothermia contained no visible areas of decreased dehydrogenase enzyme This indicated that hypothermia alone did not produce detectable myocardial injury

The incidence of arrhythmias and ventricular

hypothermia decreased oxygen demand in ischemic myocardium This is inferred from the following observations First the decrease in heart rate during hypothermia implies that minute myocardial oxygen consumption was reduced because pressure was developed fewer times each minute Blair[20] has reported that the direct effect of reduced temperature on the meta bolic rate of the myocardium causes the decline in heart rate and a parallel decrease in oxygen consumption during cooling to 25°C Second depressed contractility in hypothermic dogs indi cated by decreases in both the maximum rate of rise of left ventricular pressure (dP/dt$_m$) and the peak systolic pressure implies that the oxygen consumption during active contraction was decreased Reduced contractility has also been reported by Holobut and Stazka[?] and by Delin and associates in normal dogs cooled to compar able body temperatures However these findings conflict with reports showing a positive inotropic effect of hypothermia in normal dogs and in dogs with infarction probably because of differences in experimental conditions such as method of measuring contractility ventricular loading and level of anesthesia [23] Third lower left ventricu lar afterload (i e systemic vascular resistance) in hypothermic dogs may have contributed to a reduction in myocardial oxygen demand by decreasing cardiac minute work (external power) Since oxygen utilization is known to be higher for pressure work than for volume work hypother mic hearts probably consumed less oxygen to maintain the same cardiac index as normother mic hearts by increasing the stroke index against a reduced aortic pressure

The finding that hypothermia increased stroke index while end diastolic pressure remained unchanged suggests that the performance of the left ventricle was improved Enhanced perform ance may have resulted from decreased afterload Our results are consistent with other studies which have shown that hypothermia improves cardiac function and does not promote heart failure in dogs with myocardial infarction [?] or cardiogenic shock [?] [?]

Although hypothermia may only inhibit the necrosis of ischemic myocardium which upon rewarming will ultimately become *infarcted this* study suggests the potential value of cooling *per se* as a means of protecting the heart until a definitive procedure such as aortocoronary bypass can be initiated Maroko and colleagues have shown that ischemic myocardium in dogs at normal body temperature may be salvaged if revascularization is accomplished within 2 to 4 hours after coronary occlusion Since clinically the delay between the onset of acute ischemia and admission to surgery often exceeds 4 hours the preoperative use of whole body hypothermia might well extend the time frame within which revascularization could be successfully com pleted

Summary

Anesthetized dogs were cooled to a core body temperature of 26°C or maintained at a body temperature of 37°C during periods of 5 and 10 hours of LAD coronary artery occlusion Subse quent macroscopic dehydrogenase enzyme map ping showed that ischemic injury was 25 per cent less after 5 hours of coronary occlusion and 20 per cent less after 10 hours of occlusion in hypother mic dogs than in normothermic controls The heart rate and left ventricular minute work in hypothermic dogs *decreased to roughly half* the levels measured in normothermic animals while left ventricular contractility was 10 to 40 per cent lower in hypothermic dogs than in normothermic dogs However cardiac index and left ventricular end diastolic pressure were unchanged by whole body cooling Thus hypothermia appeared to diminish the oxygen requirements of the ischemic myocardium without reducing the performance of the heart as a pump Hypothermia may be useful as a therapeutic adjunct to myocardial revascularization or pharmacologic interven tions

The authors acknowledge the technical assistance of Mr William Voorhees and Mr William Schoenlein and the secre tarial assistance of Mrs Jane Abendschein and Miss Julie Deleo

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Table I Left ventricular end diastolic pressure

Time (hours)	*Number of dogs in each group*	*Hypothermic (mean LVEDP ± S D)*	*Normothermic (mean LVEDP ± S D)*	*Hypothermic-normothermic*	*t*	*p*
0	10	05 ± 08	05 ± 08	0	0	05
1	10	15 ± 12	15 ± 12	0	0	05
2	10	25 ± 13	08 ± 06	+17	17	>01
3	10	30 ± 18	10 ± 11	+20	16	>01
4	10	30 ± 13	25 ± 13	+05	09	>01
5	10	25 ± 13	25 ± 18	0	0	05
6	5	00 ± 00	20 ± 22	−20	10	>01
7	5	00 ± 00	10 ± 11	−10	10	>01
8	5	00 ± 00	20 ± 13	−20	16	>01
9	5	00 ± 00	10 ± 11	−10	10	>01
10	5	00 ± 00	10 ± 11	−10	10	>01

transmural area of greater pallor, containing fewer foci of stained myocardium After 10 hours of coronary occlusion, the injured area extended transmurally in both groups and the pallor of the unstained tissue was increased, but, fewer foci of stained tissue were observed in the ischemic region of normothermic dog hearts

Microscopic study of the ventricular slices after 10 hours of coronary occlusion confirmed results obtained by gross histochemical staining Few damaged cardiac muscle cells were present in NBT unstained areas of hypothermic dog hearts whereas, in normothermic dog hearts, NBT unstained areas contained numerous damaged cardiac muscle cells The histological features of damaged fibers after 10 hours of coronary occlusion consisted of hyalinized sarcoplasm with mild interstitial edema and neutrophilic infiltration Qualitatively there was no difference between hypothermic and normothermic dogs in the appearance of the damaged cells Damaged fibers could not be evaluated by light microscopy after only 5 hours of coronary occlusion

Effects of coronary occlusion and hypothermia on hemodynamics Approximately 2 hours of surface cooling was required to reduce the core body temperature to 26°C Fig 3 shows that heart rate and mean blood pressure were significantly lower in hypothermic dogs than in normothermic dogs after 2 to 3 hours of coronary occlusion Vascular resistance increased in both groups during the first 5 hours of coronary occlusion but remained lower in hypothermic dogs than in normothermic dogs

Fig 4 shows that stroke index was increased significantly in hypothermic dogs but cardiac index in the two groups did not differ significantly Left ventricular minute work was typically lower in hypothermic dogs than in normothermic dogs Fig 5 shows that both the maximum rate of rise of left ventricular pressure and the left ventricular systolic pressure were decreased by hypothermia Table I compares the left ventricular end diastolic pressure (LVEDP) in hypothermic and normothermic dogs during 10 hours of coronary occlusion LVEDP was not significantly different between the two groups

Discussion

Prevention of cardiogenic shock and death after acute myocardial infarction is largely dependent upon the containment of infarct size Since an imbalance between oxygen supply and demand in the ischemic tissue results in myocardial necrosis, interventions which improve this balance could significantly reduce the size of an infarct Thus beta adrenergic blockade with propranolol,[1] intra aortic balloon counterpulsation[19] and nitroglycerin[3] have been shown to decrease ischemic injury following coronary artery occlusion In the present study whole body hypothermia appeared to decrease the extent of ischemic injury produced by either 5 or 10 hours of coronary occlusion Histochemical staining of the sliced ventricles showed less metabolic deterioration in the ischemic region of dog hearts cooled to 26°C Histologic findings after 10 hours of occlusion were consistent with the histochemical results indicating that the morphologic tissue damage was also less in the ischemic region of hypothermic dog hearts

A possible explanation of these findings is that

Ouabain induced Wenckebach conduction block in canine Purkinje fibers The role of cycle length and time dependent changes in membrane potential

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Since Wenckebach s original description[1] of progressive conduction delay and eventual failure of conduction between atria and ventricles this type of conduction block has been described in virtually every tissue of the heart including sinus node A V junction [3] bundle of His [7] bundle branch systems [8] and ventricular tissue [8] Among the drugs likely to induce Wenckebach periods cardiac glycosides have demonstrated this well known effect in toxic doses Clinical[1] and experimental studies have verified that cardiac glycosides induce Wenckebach block in cardiac tissue most commonly in the A V junctional tissue of the intact heart Cardiac glycosides have been reported to reduce membrane potential [1 12] and thereby slow conduction velocity This effect is most likely mediated by inhibition of the sodium-potassium ATPase pump More recently studies have reported that cardiac glycosides induce low amplitude potentials delayed after depolarizations or transient depolarizations which are functions of both cycle length [5] as well as degree of toxicity [2]

While the phenomena of glycoside induced delayed after depolarizations[1] and beat to beat reduction in maximal diastolic potential[17 9] have been observed it appeared to us that these changes in membrane potential may relate to the development of Wenckebach conduction block The purpose of this report is to describe our observations on cardiac glycoside induced Wenckebach conduction block in canine Purkinje fibers Our data suggest that Wenckebach periodicity induced by cardiac glycosides is associated with a *beat to beat reduction* in membrane potential and a decrease in excitability which in turn leads to failure of conduction

Methods

Studies were conducted on adult mongrel dogs weighing 10 to 20 kilograms After anesthesia induced by sodium pentobarbital (30 mg /Kg) the heart was removed through a lateral thorax incision The heart was immediately placed in warm oxygenated Tyrode solution and dissected to obtain the desired Purkinje strand usually from the right bundle branch *system to the* papillary muscle The Purkinje strand was then placed in a plexiglass tissue chamber and superfused with warm oxygenated Tyrode solution maintained at 37 ± 0 5 C After the Purkinje strand was placed *in the* tissue chamber the two ends of the Purkinje strands were pinned for immobilization The composition of the Tyrode solution in millimoles *was as follows*

NaCl	137 0	$NaHCO_3$	12 0
KCl	2 7	Glucose	5 5
MgCl	0 5	$CaCl_2$	2 7
NaH_2PO	1 8		

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Supported b th C rdio ascula Instit te Research Fu d South astern Pennsylvan H rt Association

Recei ed for publ ation J 24 19 8

Accepted f publication Apr 12 19'8

Reprint req est C ry J Anderson M D Th W lliam Lik ff Card o ascul Inst tut H hnem n Medi l College a d Hospital, 230 North Broad St eet, Phil delphia PA 19102.

Dr Reiser is U S P H S Postdoct ral F llow

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Ouabain induced Wenckebach conduction block in canine Purkinje fibers The role of cycle length and time dependent changes in membrane potential

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Since Wenckebach s original description[1, 2] of progressive conduction delay and eventual failure of conduction between atria and ventricles, this type of conduction block has been described in virtually every tissue of the heart including sinus node A V junction[4, 5] bundle of His[6, 7] bundle branch systems[8] and ventricular tissue[6] Among the drugs likely to induce Wenckebach periods cardiac glycosides have demonstrated this well known effect in toxic doses Clinical and experi mental studies have verified that cardiac glyco sides induce Wenckebach block in cardiac tissue most commonly in the A V junctional tissue of the intact heart Cardiac glycosides have been reported to reduce membrane potential and thereby slow conduction velocity This effect is most likely mediated by inhibition of the sodi um-potassium ATPase pump[1] More recently studies have reported that cardiac glycosides induce low amplitude potentials delayed after depolarizations or transient depolariza tions which are functions of both cycle length as well as degree of toxicity[16 o]

While the phenomena of glycoside induced delayed after depolarizations[3, 9] and beat to beat reduction in maximal diastolic potential[7, 20] have been observed it appeared to us that these changes in membrane potential may relate to the development of Wenckebach conduction block The purpose of this report is to describe our observations on cardiac glycoside induced Wenckebach conduction block in canine Purkinje fibers Our data suggest that Wenckebach perio dicity induced by cardiac glycosides is associated with a beat to beat reduction in membrane potential and a decrease in excitability which in turn leads to failure of conduction

Methods

Studies were conducted on adult mongrel dogs weighing 10 to 20 kilograms After anesthesia induced by sodium pentobarbital (30 mg /Kg) the heart was removed through a lateral thorax incision The heart was immediately placed in warm oxygenated Tyrode solution and dissected to obtain the desired Purkinje strand usually from the right bundle branch system to the papillary muscle The Purkinje strand was then placed in a plexiglass tissue chamber and super fused with warm oxygenated Tyrode solution maintained at 37° ± 0 5° C After the Purkinje strand was placed in the tissue chamber the two ends of the Purkinje strands were pinned for immobilization The composition of the Tyrode solution in millimoles was as follows

NaCl	137 0	$NaHCO_3$	12 0
KCl	2 7	Glucose	5 5
MgCl	0 5	CaCl	2 7
NaH PO	1 8		

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Supported by the C rdiovascul r Inst tute Resear h Fund South ast ern Pe nsyl n H art Association.

Received for public tion J n. 24 19'8

Accepted for publ tion Apr 1., 19'8

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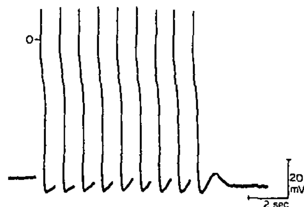


Fig 1 Effect of ouabain (2 × 10 M) on the diastolic potential (phase 4) of the Purkinje fiber paced in a train of nine stimuli at a basic cycle length (BCL) of 1 000 msec Each train was followed by a pause of 5 seconds After 26 minutes of ouabain superfusion a progressive increase in the diastolic slope was noted with successive beats in the stimulus train This increase in the diastolic slope was expressed as an after depolarization following the last beat of the stimulus train (Photograph retouched)

Conventional microelectrode techniques were employed as described elsewhere [6]

Glass microelectrodes were utilized with tip resistances ranging between 15 to 20 megohms Extracellular stimulation was accomplished by placing Teflon coated stainless steel electrodes bared at the tip on one end of the Purkinje strand Stimuli were provided by a specially constructed interval and pulse generator * The sweep generator of the oscilloscope was synchronized to the stimulator Current threshold requirements were determined by employing an intracellular stimulating and recording system [1] Intracellular stimulation and recording was accomplished by utilizing a switching system in which the same microelectrode could be used for both current threshold determination and recording of intracellular action potentials Upon activation of the switching system the microelectrode was used for current threshold determination while the amplifier of the microelectrode was shorted to ground After termination of the current pulse the switch was again activated and the microelectrode was employed for action potential recording Current was recorded by closing the current pulse circuit to ground via the input resistance of the oscilloscope During the stimulation train *extracellular* stimulation was performed except for one or two beats in which intracellular stimulation was performed Extracellular stimulation intensity was maintained at twice threshold and intracellular current threshold was recorded when any given current intensity yielded activation 50 per cent of the time or more

Data were recorded simultaneously on a Tektronix 5113 memory oscilloscope for Polaroid photography and on a Honeywell 7600 analog tape recorder for permanent data storage

The tissue was superfused with ouabain (2 0 × 10 M) until the cells developed delayed after depolarizations at which time the membrane potential ranged from −60 mV to −75 mV Ouabain concentration was then reduced to 1 1 × 10 ⁷M to sustain the desired effects

Results

Since we will attempt to develop a postulate for Wenckebach periodicity based upon beat to beat changes in action potential parameters it would facilitate understanding of subsequent data if data dealing with beat to beat changes were presented Fig 1 is representative of such an example The tissue was stimulated in trains of 9 at a basic cycle length (BCL) of 1 000 msec followed by a 5 second pause and recycled again to a train of 9 Data were recorded after 26 minutes of superfusion with ouabain The first action potential terminating the 5 second pause is seen at the left which is followed by 6 mV/sec of phase 4 depolarization The slope of diastolic depolarization progressively increases until the ninth applied stimulus The difference between the maximal diastolic potential of the ninth beat and the membrane potential at the point of application of the stimulus was 8 mV and the slope of diastolic depolarization increased to 18 mV/sec Following cessation of stimuli a delayed after depolarization is seen which repolarizes to a potential of −82 mV The progressive increase in the slope of phase 4 depolarization with successive beats effectively results in a progressive decrease in the membrane potential from which the action potential arises (or take off potential) Data similar to this has been previously reported [17, 9]

Since one of the well known effects of cardiac glycosides is inhibition of the sodium-potassium pump [13, 14] it was anticipated that stimuli applied sufficiently rapidly might result in depolarization

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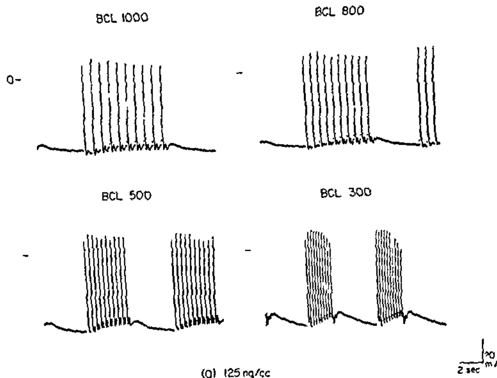


Fig 2 Effect of cycle length on Purkinje fibers exposed to toxic concentrations of ouabain All sequences were recorded consecutively after 35 minutes of ouabain exposure (2 × 10 M) Stimuli were applied in trains of ten (10) at decreasing cycle lengths (BCL) of 1 000 800 500 300 respectively Following each train of stimuli a 5 second pause was interposed Note the progressive reduction in the maximum diastolic potential with successive beats in the trains of decreasing cycle lengths In addition a direct relationship of cycle length and repolarizing slope of the diastolic potential during the 5 second pause is indicated

of the cell possibly mediated by either an increase in intracellular sodium (Na,) or outside potassium (K) In the studies by Hogan and colleagues increasing the stimulation rate from 60 beats/minute to 120 beats/minute resulted in a reduction of the maximal diastolic potential of ouabain treated Purkinje fibers When the rate was then returned to 60/minute a gradual increase in membrane potential was observed We have extended these studies and programmed pauses into trains of stimuli to more precisely identify beat to beat changes in maximal diastolic potential and membrane potential changes in prolonged diastolic periods as dependent on cycle length of stimulation Fig 2 shows data recorded from an experiment in which stimuli were applied in trains of ten at different basic cycle lengths After each train of ten a pause of 5 seconds was interposed and the train of ten stimuli was repeated Data for all cycle lengths were recorded within 2 minutes The Purkinje strand was initially superfused with ouabain (2 0 × 10 M) for 35 minutes At a basic cycle length of 1 second the maximal diastolic potential of the first action potential (MDP) was −84 mV (Fig 2) After the sixth action potential maximal diastolic potential was reduced to −80 mV and remained at −80 mV through the tenth beat the difference in maximal diastolic potential between the first and tenth beat (MDP_1−MDP_{10}) was 4 mV At a basic cycle length of 800 msec MDP_1 was −84 mV and MDP_{10} was −76 mV As the basic cycle length was shortened the degree of depolarization occurring with successive stimuli was increased The observation that shorter cycle lengths produced a more marked reduction in maximal diastolic potential was also noted at lesser degrees of toxicity However more rapid stimulation was required to produce these changes in maximal diastolic potential

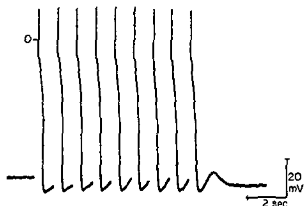


Fig 1 Effect of ouabain (2×10^{-7}M) on the diastolic potential (phase 4) of the Purkinje fiber paced in a train of nine stimuli at a basic cycle length (BCL) of 1 000 msec Each train was followed by a pause of 5 seconds After 26 minutes of ouabain superfusion a progressive increase in the diastolic slope was noted with successive beats in the stimulus train This increase in the diastolic slope was expressed as an after depolarization following the last beat of the stimulus train (Photograph retouched)

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The tissue was superfused with ouabain (2.0×10^{-7}M) until the cells developed delayed after depolarizations at which time the membrane potential ranged from −60 mV to −75 mV Ouabain concentration was then reduced to 1.1×10^{-7}M to sustain the desired effects

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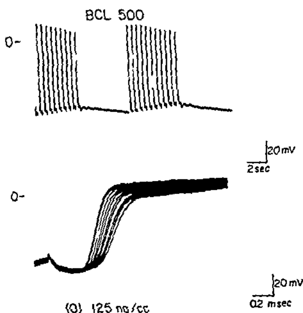


Fig 4 Ouabain induced alteration of action potential configuration (top) and phase 0 (bottom) during a stimulus train Both sequences in this figure are representative of the same cell, recorded simultaneously at different sweep speeds on separate oscilloscopes After 39 minutes of ouabain exposure (2 × 10 M) the characteristic decrease in the maximum diastolic potential during the stimulus train is shown *in the top trace* (slow sweep speed) concomitant to the decreasing diastolic potential the action potential amplitude decreased with successive beats in the trains of 10 beats *In the lower sequence* only the action potential upstroke (phase 0) is shown due to the expanded sweep speed The initial portion of the sweeps includes the stimulus artefact A decrease in the slope of phase 0 with successive beats is demonstrated

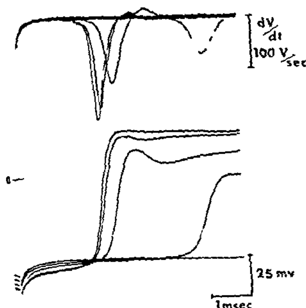


Fig 5 Effect of ouabain on activation time of successive beats during a stimulus train The sweep speed was expanded as in the previous figure Only the upstroke (phase 0) of the action potential is indicated (bottom trace) and its corresponding derivative (dV/dt *top trace*) Stimulating and recording electrodes were sufficiently separated thus accounting for the initial latency (activation time) between the stimulus artefact and initiation of the action potential Both an increase in the activation time and an associated decrease in dV/dt is demonstrated with successive beats reflecting a Wenckebach periodicity Calibration of dV/dt is 100 V/sec (Retouched from original photography)

beat was 98 mV and was reduced to 68 mV by the ninth The tenth applied stimulus (not identifiable in the figure) failed to induce a propagated response and a spontaneous beat is noted early in the 5 second pause The amplitude of this spontaneous beat is increased from the previous action potential to 93 mV and occurs after a cycle length of 1 200 msec These data demonstrated two interesting phenomena occurring in ouabain intoxicated Purkinje fibers In fibers exposed to ouabain the first observed response is the disappearance of phase 4 during the programmed pause and the appearance of hyperpolarization Second during intermittent trains of stimuli beat to beat depolarization is more pronounced with increasing exposure time to ouabain

The observation that the cells exposed to ouabain depolarized on a beat to beat basis with stimulation suggests that concomitant changes in phase 0 might be observed with an increased sweep speed Fig 4 shows the slow and rapid sweep displays of ten sequentially applied stimuli and subsequent action potentials recorded from a Purkinje fiber after a 5 second pause The preparation had been exposed to ouabain for 39 minutes The Purkinje strand was stimulated at a basic cycle length of 500 msec The maximal diastolic potential following the first beat was −73 mV and action potential amplitude was 88 mV With each successive stimulus action potential amplitude and maximal diastolic potential decreased until the tenth action potential which had an action potential amplitude of 71 mV (Fig 4 *top*) At a rapid oscilloscope sweep speed (0 2 msec/cm) the successive phases 0 show progressive reduction in the rate of rise of phase 0 (dV/dt) Phases 0 of the first two beats were superimposed and thereafter showed the progressive reduction in dV/dt as well as delay in

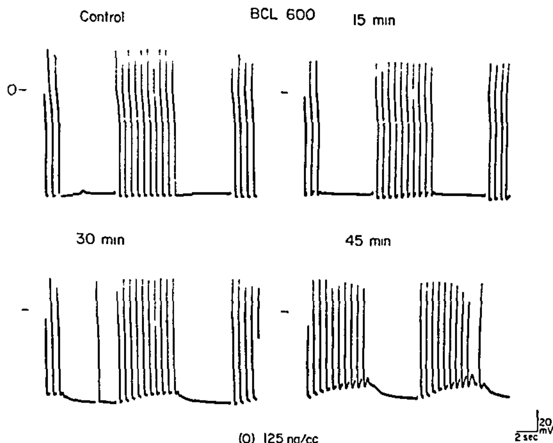


Fig 3 Time dependence of ouabain induced alterations of membrane potential in Purkinje fibers paced by a stimulus train interrupted by a 5 second pause The basic cycle length was maintained constant in all sequences (BCL = 600) In the control sequence no significant changes in the maximum diastolic potential are observed At 15 minutes of ouabain exposure (2 × 10 M) a gradual decrease in the maximum diastolic potential with successive stimuli is noted In addition a small after depolarization develops at the point of initiating the 5 second pause The changes in membrane potential became exaggerated both at 30 minutes and 45 minutes of ouabain superfusion A progressive increase of the repolarizing slope of the membrane potential (during the 5 second pause) as a function of the duration of ouabain exposure is demonstrated

The reduction in diastolic membrane potential after exposure to cardiac glycosides is thought to be due to inhibition of the sodium pump Increasing the exposure time to ouabain produces an expected further reduction of diastolic membrane potential both in response to abrupt increases in stimulation rate and at slower intermittent pacing (Fig 3) At a basic cycle length of 600 msec in the control state depolarization did not occur with trains of ten Maximal diastolic potential after the first action potential was −93 mV and remained at that potential through the tenth action potential Phase 4 depolarization was noted to some degree during the 5 second pause and resulted in a 3 mV reduction in membrane potential With exposure to ouabain a beat to beat reduction in maximal diastolic potential was noted At 15 minutes MDP after the first action potential was −93 mV Following each action potential the slope of phase 4 progressively increased through the fifth action potential and maximal diastolic potential is reduced to −90 mV by the tenth beat During the 5 second pause membrane potential remained at −90 mV until the return of the stimulation At 30 minutes membrane potential at the time of application of the first stimulation was −83 mV MDP was reduced following each action potential and after the tenth action potential a delayed after depolarization was observed followed by a repolarization of membrane potential from −74 mV to −83 mV A similar sequence of events was noted at 45 minutes In the first train of ten beats maximal diastolic potential was reduced from −78 mV after the first beat to −66 mV after the tenth beat However in this train the action potential amplitude of the sixth beat was reduced and continued to decrease in amplitude until the tenth beat Repolarization following the tenth beat from −66 mV to −76 mV occurred during the 5 second pause and the train of ten was repeated Action potential amplitude of the fifth

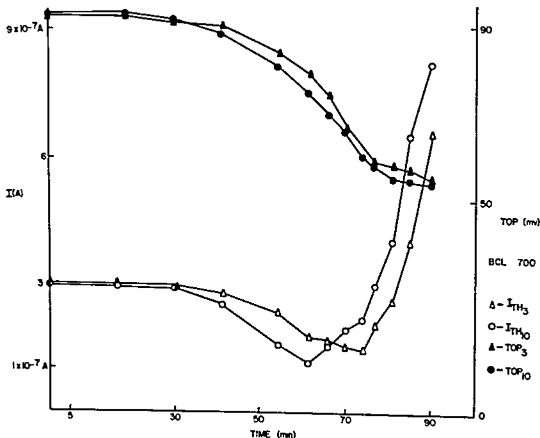


Fig 7 Graph showing the relationship of current threshold and take off potential with successive beats during ouabain exposure *Abscissa* duration of ouabain (2 × 10 M) superfusion *Ordinate (Left)* magnitude of current to reach threshold (amperes) *Ordinate (Right)* membrane potential (mV) at which the action potential arose Threshold current was measured at beat 3 (I *open triangles*) and beat 10 (I *open circles*) in a train of 10 beats (BCL = 700) during ouabain superfusion *Solid triangles and circles* denote the corresponding take off potential of the third (TOP) and tenth (TOP) beat respectively See text for further discussion

follows Initially take off potential and current threshold are similar for both the third and tenth beats TOP and I_{th} first decreased followed by a decrease in TOP and I_{th} I_{th} then increased followed by an increase in I_{th3} It is interesting to note that the increase in I_{th0} occurred at a membrane potential of −74 mV while the increase in I_{th} occurred at a membrane potential of −60 mV After 90 minutes Wenckebach periods occurred and trains of ten stimuli failed to elicit the full sequence of ten propagated action potentials This response was observed in five of five experiments

Discussion

Several hypotheses have been proposed for Wenckebach conduction and include decremental conduction encroachment upon the refractory period of the preceding impulse and electronic transmission through a site of conduction block[2] The mechanism for Wenckebach block however has not yet been resolved to a point of unanimous agreement

Many recent reports have cited the electrophysiological manifestations of glycoside toxicity in Purkinje fibers Our study has repeated many of these studies in an attempt to relate the previously identified glycoside induced changes with changes in excitability and conduction Our data suggest that the glycoside induced Wenckebach periods are related to the delayed after depolarizations and concomitant changes in excitability Recent reports have described changes in phase 4 of Purkinje fibers which have been termed transient depolarizations delayed after depolarizations or low amplitude potentials[16 1] These delayed after depolarizations were observed in the course of induction of cardiac glycoside toxic

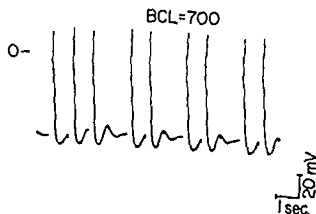


Fig 6 Beat to beat variation in the after depolarization following ouabain superfusion Basic cycle length is constant at 700 msec The Purkinje fiber was exposed to ouabain for 39 minutes With successive beats a progressive increase in the diastolic slope can be noted expressed as an after depolarization Although external stimulation was maintained the action potential was consistently blocked concomitant with the largest after depolarization The periodic block resulted in varying conduction patterns which tends to repeat in a cyclic fashion See text for further discussion

activation time The gradual reduction in membrane potential results in a thickening of the trace following the stimulus artefact

Fig 5 represents an example in which the recording and stimulating electrodes were more separated These data were recorded from a Purkinje cell exposed to ouabain for 44 minutes The basic cycle length of stimulation was 500 msec The first applied stimulus elicits an action potential after 2 4 msec The take off potential was −66 mV and the dV/dt was recorded to be 195 V /sec The second applied stimulus elicits a response of 2 6 msec and its corresponding dV/dt is 167 V /sec The increase in activation time was 0 2 msec The third applied stimulus elicits a response after 2 9 msec and dV/dt is further reduced to 124 V /sec The fourth applied stimulus induced a response with a conduction time of 5 7 msec and dV/dt of 73 V /sec The fifth and sixth applied stimuli failed to induce a propagated response The conduction pattern observed was that of Wenckebach conduction block Fig 6 shows the relationship between the beat to beat changes in the slope and height of delayed after depolarizations and the eventual development of a blocked beat The first action potential arises from a membrane potential of −72 mV Following this action potential, the slope of the diastolic period results in a reduction in membrane potential to −70 mV at the point of stimulus application Following the second action potential the delayed after depolarization is more prominent and membrane potential is further reduced to −65 mV at the time of application of the third stimulus Following the third action potential, the delayed after depolarization is larger and results in a further reduction in membrane potential The stimulus is applied after the peak of the delayed after depolarization and is associated with failure to produce a propagated response to the recording electrode This pattern of 4 3 conduction reverted to 3 2 conduction as shown in the remainder of the rhythm strip

Changes in excitability The observed changes in both membrane potential and phase 0 with successive beats suggest that changes in excitability might also occur To test this hypothesis we designed experiments in which the current threshold for stimulation could be quantitated Fig 7 presents data from one such experiment in which the tissue was superfused with ouabain (2×10^{-7}M) and stimulated at a basic cycle length of 700 msec in trains of ten followed by a 5 second pause Membrane potential at the onset of the action potential, the so called take off potential (TOP) is plotted for the third (TOP_3) and tenth (TOP_{10}) action potentials as was the current threshold (I_{th}) in amperes for the third (I_{th3}) and tenth (I_{th10}) action potentials Control take off potential of the third action potential was −92 mV Control current threshold values for the third and tenth beats were identical at 3×10^{-7}A Superfusion with ouabain did not significantly alter TOP or I_{th} until 40 minutes at which time TOP_3 was −91 mV and TOP_{10} was −89 mV I_{th3} was slightly reduced and I_{th10} was reduced even more, suggesting that the membrane potential of the tenth beat was closer to threshold and hence more excitable Continued superfusion with ouabain resulted in further decreases in current threshold requirements until 60 minutes at which time I_{th10} began to increase and by 67 minutes was equal to that of I_{th3} Once I_{th10} exceeded I_{th3} it remained greater although at 73 minutes I_{th3} also increased but for any given time was less than I_{th10} Membrane take off potential of the tenth beat was less than the third after 33 minutes Take off potential of the third beat also decreased but the exposure time required to attain any given membrane take off potential was longer than for the tenth beat

In summary Fig 7 shows sequential changes as

accumulation outside the membrane increases potassium conductance and that this effect is greater by the tenth beat than for the third Current threshold may thereby increase since sodium conductance must exceed potassium conductance to produce excitation

The observed decrease in maximal diastolic potential with increasing rate of stimulation in Purkinje cells exposed to ouabain (Fig 2) suggests that the well known ability of cardiac glycosides to inhibit Na -K ATPase [3] plays a role in this depolarization At slower rates of stimulation accumulation of sodium inside and/or potassium outside may not occur possibly because the sodium pump can adequately handle the required ion pumping At higher rates of stimulation accumulation of these ions may occur which cannot be adequately transported by the available pumping sites Such an accumulation of these ions such as K outside may lead to temporary shifts in membrane potential which with sufficient periods of quiescence may further repolarize (Fig 3) to control levels The positive shift in membrane potential occurring in our studies may represent the combined effects of the progressive increase in the slope of phase 4 depolarization and the local accumulation of potassium outside the membrane An accumulation of sodium inside may also induce depolarization but the quantity of sodium flux associated with depolarization would be unlikely to shift the membrane potential several millivolts as noted in these experiments

Our data describe physiologic responses in Purkinje cells exposed to ouabain which provide a basis for the observed progressive slowing of conduction in Wenckebach periodicity That this mechanism is operative in the A V junction is not necessarily implied since the electrical properties of A V junctional cells are so dissimilar from those of Purkinje fibers

Summary

The purpose of this study was to determine the mechanism for digitalis induced Wenckebach conduction block Canine Purkinje cells were exposed to ouabain (2 0 × 10 M) and studied with conventional microelectrode techniques When trains of stimuli were interrupted by a 5 second pause restoration of stimuli resulted in successive action potentials showing an increasing slope of phase 4 depolarization which was expressed after the last beat as a delayed after depolarization For any given state of ouabain toxicity a beat to beat reduction in maximal diastolic potential could be induced by shortening the basic cycle length If basic cycle length remained constant continued exposure to ouabain would increase the net voltage reduction in membrane potential occurring during the train of ten beats During the 5 second pause an increase in membrane potential was observed and this hyperpolarization was of the same magnitude as the depolarization occurring during stimulation With successive beats as membrane potential was reduced action potential amplitude and dV/dt were concomitantly reduced and conduction slowed Intracellular current threshold measurements showed that the reduction in membrane potential initially was associated with decreased current threshold requirements but later in toxicity current threshold was markedly increased for beats occurring late in the train These data suggest that (1) the beat to beat reduction in membrane potential is due to both an increase in the height of the delayed after depolarization and a reduction in maximal diastolic potential (2) trains of beats are associated with progressive prolongation of activation time with concomitant reduction in dV/dt and membrane potential and (3) failure of conduction is probably related to Purkinje segments showing decreased excitability

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ity The heights of the delayed after depolarizations have been correlated with cycle length[19] *Data has also been recorded*[17, 19] showing that with stimuli applied in trains, the slope of phase 4 depolarization (or the ascending limb of the delayed after depolarization) progressively increased similar to that observed in Fig 1 This increase in the diastolic slope results in a decrease in the membrane potential at the time of application of the stimulus Accordingly, the take off potential *is progressively reduced, and occurs* with a concomitant reduction in dV/dt as shown in Fig 4 These data suggest that both the reduction in membrane potential and dV/dt may play a role in the progressive reduction in conduction velocity of successive impulses The studies of Rosen and associates[30] and Saunders and colleagues[16] have shown data consistent with this hypothesis These studies demonstrated the relationship of the delayed after depolarizations and the success or failure of a critically timed premature impulse *When the premature impulse was* applied on either side of the peak of the delayed after depolarization propagation to ventricular muscle occurred However, application of the impulse close to the peak of the delayed after depolarization resulted in conduction block

As noted above cardiac glycosides reduced the take off potential by increasing the slope of phase 4 and by reducing the maximal diastolic potential This possibly relates to our observation on the biphasic current threshold response of *Purkinje cells exposed to ouabain Early in the* course of glycoside administration there was an initial reduction in take off potential in which the take off potential of the tenth beat was usually less negative than the third beat This may be accounted for on the basis of an increasing slope of phase 4 following the ninth action potential compared to the second Presumably threshold potential has not been likewise reduced and therefore current threshold is less for the tenth beat than for the third Later in the time course of glycoside administration the continued application of stimuli in trains of ten induced changes in membrane parameters tending to make the current threshold *requirements for* the tenth beat higher than the third The explanation for these phenomena might rest in the combined effects of the cardiac glycoside on the delayed *after depolarizations* and Na -K pump inhibition In more severe degrees of toxicity, the reduction in membrane potential due to increased pump inhibition with successive beats is greater and the resulting cation accumulation (either K_o[31, 3] or Na_i) would be greater In such circumstances the degree of sodium inactivation may in fact be greater with the tenth beat than for the third Thus, the slight reduction in *take off potential of* the third beat narrows the margin between the cells' membrane potential and threshold poten*tial, thereby reducing current threshold* requirements However, with each subsequent beat, both the *slope of phase 4 increases and presumably* sodium inactivation is increased Concomitant with the reduction in membrane potential threshold potential is reduced Presumably the threshold potential is shifted to a greater extent, thereby increasing the separation between mem*brane potential and threshold potential* This in turn, increases current threshold requirements The observed increase in current threshold for excitability *may relate to the mechanism for* conduction block in Wenckebach periods If a segment of a Purkinje strand has decreased excitability, then it would favor the development of Wenckebach periodicity This area of increased current threshold may develop if a segment of Purkinje was more susceptible to cardiac glycosides or was affected by underlying preexistent disease Our data however, do not indicate which of the two mechanisms may be responsible for the beat to beat changes in current threshold re*quirements for excitation* From the above discussion we may note that both voltage dependent changes in excitability may occur as well as those occurring secondary to ion conductance changes and pump inhibition The relative contribution of each of these factors to the observed Wenckebach block requires further study

The finding that current threshold increased at different membrane potentials for the third and tenth beats (Fig 7) was noteworthy In *all five* experiments the third beat depolarized to less negative values before an increase in current threshold was observed This finding is not explained solely by sodium inactivation as postulated above Since the increase *in current threshold* occurs at a more negative membrane potential for the tenth beat it is suggested that a *parameter for* threshold potential is not membrane potential alone It is possible that K

Endocardial fibroelastosis Myocardial and vascular alterations associated with viral like nuclear particles

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The pathogenesis of primary endocardial fibroelastosis (EFE) remains an enigma despite an increasing body of clinical immunologic[6] and experimental evidence accumulated over the past two decades implicating viral myocarditis in the development of this condition The viruses considered to be the most likely agents include mumps and coxsackie In general histopathologic findings in EFE have not conclusively supported an infectious etiology Even in those cases presumed to be of infectious origin the observed lesions have included non specific foci of calcification fibrosis vascular sclerosis and rare inflammatory infiltrates[2] Since viral inflammation may resolve completely and leave only structural damage as a clue to pre existing infection (i e rubella) it should not be surprising that viral particles or specific lesions attributable to viruses have never been demonstrated in primary EFE

The present report describes in detail the light microscopic and ultrastructural features of the myocardium in a case of primary EFE A possible relationship to viral myocarditis was supported by the observation of unusual intramyocardial small vessel endothelial proliferation myocardial cellular alterations and intranuclear particles suggestive of viral associated material

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Received for publication Oct 13 1977

A cepted f r pu l tio Nov 14 19

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Case report

An 8-month-old male infant was admitted to the hospital in respiratory distress There was no history of previous respiratory or cardiac ailments. Physical examination revealed a tachypneic febrile infant with a tachycardia of 200/minute Auscultation of the lungs and heart was unremarkable Hepatomegaly was present Chest roentgenogram demonstrated a markedly enlarged cardiac silhouette Electrocardiogram revealed left axis deviation high QRS voltage in Leads V V_6, notched P waves and P mitrale Following 4 hours of treatment with digitalis oxygen and diuretics the patient had a cardiopulmonary arrest Resuscitation attempts were unsuccessful

Postmortem examination was performed 16 hours after death. With the exception of pulmonary and visceral congestion abnormalities were limited to the cardiovascular system The heart weighed 112 grams (normal 37 grams) and was globular in shape All four chambers were dilated and both the left and right ventricular walls were hypertrophied The left atrial and left ventricular endocardial surface was pearly white in color and measured up to 2 mm in thickness Papillary muscles were encased in the fibroelastic tissue Focal fibrous septa were noted to extend from the endocardium into the underlying muscle Cardiac valves and chordae tendineae were structurally normal however the mitral and tricuspid valves were irregularly thickened Coronary arteries were of normal caliber and arose from the aorta

Materials and methods Routine paraffin embedded sections were prepared from all four cardiac chambers and valves Tissue was stained with hematoxylin and eosin periodic acid Schiff with and without pretreatment with diastase elastic van Gieson and Masson s trichrome Specific attention was given to the degree and type of myofiber abnormalities the presence of interstitial fibrosis not associated with extension of overlying endocardial fibroelastotic tissue into the myocardium in the form of septa or involving arterio luminal vessels the presence of inflammation and the extent if any of vascular alterations.

Sections for electron microscopy were prepared from tissue which had been fixed in 3 7 per cent formaldehyde for 4 days Segments of fibroelastotic left ventricular endocardium and underlying myocardium were removed and diced into 1 mm

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Fig 2 Dense interstitial collagen diffusely surround atrophic myocardial cell Numerous clear vacuoles are present within many myofibers in some cases comprising a significant proportion of the cell diameter (*arrows*) (Trichrome stain original magnification ×63)

exception of one arteriole which had a round cell inflammatory infiltrate within its wall no intramural inflammation was associated with the cellular proliferation

Chronic inflammatory cells were diffusely scattered throughout the interstitium and were only rarely aggregated into focal collections The infiltrate consisted predominantly of lymphocytes histiocytes rare plasma cells and typical Anitschkow myocytes (Fig 4) The cells were noted particularly beneath the endocardium around blood vessels in areas of dense interstitial fibrosis and within the mitral valve substance Minimal inflammation was seen in the surface endocardium

Two segments of peripheral striated muscle were available for study Of special interest changes similar to those in the myocardium were observed particularly interstitial and perivascular inflammation focal fibrosis and partial obliteration of arteriolar lumens by proliferated intimal cell (Fig 5) No other similar microscopic inflammatory changes were demonstrated in any other organs

Electron microscopy Ultrastructural alterations were observed in the interstitium and in individual myocytes Endothelium of capillaries and small arterioles demonstrated a pronounced degree of cytoplasmic swelling with numerous small projections extending into the vessel lumen in many cases leading to complete occlusion (Fig 6) Small electron dense particles and increased numbers of surface pinocytotic vesicles were noted within the projections Nuclei were abnormal and will be described below The surrounding interstitium had proliferation of basal lamina presence of increased collagen, and cellular debris.

Myocytes had increased numbers of mitochondria many with bizarre and irregular sizes and shapes (Fig 7) Intracellular cytoplasmic vacuoles were frequently observed and were of two types In the paranuclear zone large single membrane delimited vacuoles were present containing coarsely granular electron dense material Cytoplasmic organelles were usually absent from these structures In the second type of vacuole cytoplasmic material including intact or degenerated mitochondria membranous whorls, and lysosomes were seen (Fig 8) These vacuoles were of variable size and in some areas were clearly delimited by a double unit membrane Similar vacuoles with a double lining have been reported in vascular smooth muscle cells and myocardium and have been interpreted as cell to cell hernias Foci of myocellular degeneration with severe disruption of cellular morphology were noted (Fig 9) and areas of myofibrillolysis were commonly observed With the exception of clearing of the mitochondrial matrix there was no suggestion that the alterations in the zones of degeneration were secondary to tissue autolysis

Within otherwise hypertrophied and irregular myocardial nuclei as well as less commonly within endothelial nuclei diffuse and aggregated viral like particulate elements were observed (Figs 10 and 11) These nuclear inclusions were smaller than nucleoli and were less electron dense than chromatin They were composed of numerous round bodies measuring 25 to 85 nm in diameter Tubular structure or crystalline arrays were never seen Although poorly defined there was an indication of a fuzzy coat around the outer margin of some individual bodies and in several instances a dense inner core could be discerned (Fig 11) Particularly

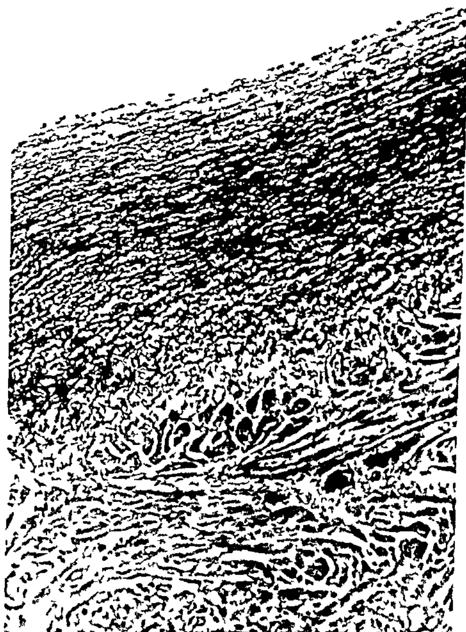


Fig 1 A representative section from the left ventricular endocardial surface The thickened endocardium (*top*) is composed of coarse elastic fibers (*stained dark*) and collagen (*stained light*) In this region there is minimal penetration of the fibroelastosis into the underlying myocardium (Elastic van Gieson stain original magnification ×63)

cubes The tissue was washed in cacodylate-sucrose buffer pH 7 4 for 2 hours post fixed in osmium tetroxide for 2 hours dehydrated in progressively increasing concentrations of alcohol and propylene oxide and embedded in epoxy resin One micron sections stained with alkaline toluidine blue were examined to select appropriate areas for study Ultrathin sections were prepared with diamond knives mounted on copper grids and stained with uranyl acetate and lead citrate Grids were examined in RCA EMU 3C and Siemens Elmiskop IA electron microscopes

Light microscopy The left atrial and ventricular endocardial surface was composed of fine and coarse elastic fibers and collagenous tissue (Fig 1) Focally groups of trapped vacuolated myofibers and conduction tissue were incorporated into the sclerotic endocardium Myofibers generally were hypertrophied with increased cellular diameter and hyperchromatic bizarre and rectangular nuclei Clear intracytoplasmic vacuoles could be appreciated in almost every muscle cell Intranuclear vacuoles were also present but no typical inclusion bodies were seen A diffuse network of loose pericellular collagen extended transmurally within the interstitium In irregular foci dense collagenous tissue surrounded atrophic myofibers (Fig 2) Virtually all small and medium sized blood vessels were surrounded by proliferated adventitial fibrosis which extended focally into the interstitium

Within the superficial and midwall myocardium many small arteries were completely occluded by vacuolated intimal cells (Fig 3) The internal elastica and the media were usually intact however bubbly basophilic material resembling mucopolysaccharide was present in some vessel walls Occlusive intimal proliferation was noted in occasional small arterioles however it was difficult to evaluate smaller vessels With the

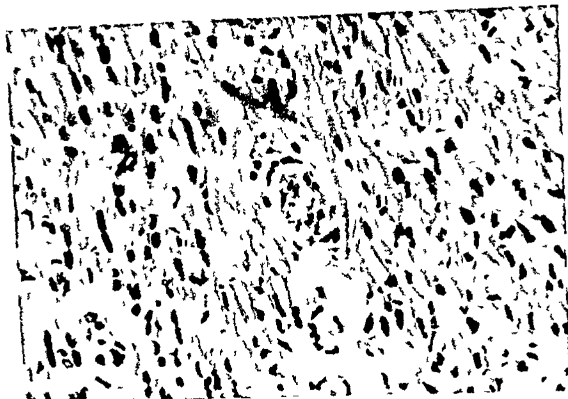


Fig 4 Numerous darkly stained inflammatory cells are present within the myocardial interstitium A small artery (A) in the center is surrounded by similar cells The vessel lumen is partially occluded by intimal cells (Hematoxylin-eosin stain original magnification ×100)

and EFE has been derived from two models Round heart disease of turkeys a spontaneous myocarditis appearing in susceptible birds [10] results in cardiac hypertrophy left ventricular dilatation and EFE with features remarkably *similar to the human disease* Microscopically focal interstitial inflammation was observed in birds under 1 month of age with progressive condensation of subendocardial collagen and elastic tissue and diminution of inflammation as the birds matured Ultrastructurally various degenerative phenomena and spherical viral like particles were described in affected and normal cell These particles measuring 60 to 90 nm with a central dense core of 30 to 60 nm resembled avian leukosis virus according to the authors In contrast to the mechanical dilatation hypothesis fibroelastotic deposition in the turkey heart appears to precede the development of overt ventricular dilatation

St Geme and associates have inoculated chick embryos with mumps virus They described features of myocarditis which subsided following hatch and at one year of age histological fibroelastosis was present in the endocardium of the left ventricle In both the chick and turkey models (similar to the human disease) EFE was present in young birds without significant evidence of myocardial inflammation

This report represents the first study of a human case of idiopathic EFE in which extensive myocardial degeneration and vascular abnormalities consistent with viral infection have been associated with viral like particles in endothelial and myocardial cells Although viral culture was not performed in this case and tissue was not available for immunologic confirmation of the viral nature of the observed particles their presence in areas of myocardial degeneration and endothelial proliferation their lack of resemblance to known artifact or *non viral spherical* microparticles and their morphologic similarity to confirmed viral structures [6] or supposed viral related material [3] support the view that they are of viral origin

At the light microscopic level several alterations suggested an infectious etiology Extensive interstitial fibrosis was associated with mononuclear inflammation Degenerative changes were prominent with myofiber atrophy and extensive



Fig 3 An intramyocardial artery is completely occluded by vacuolated intimal cells (*IC*). A portion of the internal elastic membrane (*arrow*) may be seen. Surrounding the vessel there is relatively acellular perivascular fibrosis (*PVF*) with collagen (*C*) extending into the myocardial interstitium. Myofibers are atrophic. (Elastic van Gieson stain, original magnification ×250)

within endothelial nuclei, the viral like particles were not aggregated but were focally dispersed throughout the nucleoplasm. Additionally, the structures were also present along the outer nuclear envelope and were within cytoplasmic fragments located in the interstitium.

Discussion

Renewed interest in the infectious etiology of endocardial fibroelastosis was stimulated by Noren and associates[6] in 1963. They described a group of patients having cutaneous delayed hypersensitivity to mumps virus antigen associated with an increased frequency of maternal exposure to mumps virus during the first trimester of pregnancy. This immunologic and epidemiologic study and subsequent reports[7,8] reversed a trend of approximately 25 years during which time mechanical and hemodynamic forces were invoked by most investigators[1-4] to explain the pathogenesis of this disorder. Although observers in the 1930's had interpreted pathologic features seen in EFE such as myocardial fibrosis, calcification, rare inflammatory foci, and vascular sclerosis as indicative of *in utero* infection, these abnormalities were subsequently discounted as nonspecific alterations. Despite the fact that many of the theories invoked to explain the development of EFE had basic conceptual flaws (see Schryer and Karnauchow for a review), it was not until the techniques of clinical immunology, electron microscopy, and experimental viral endomyocarditis were applied to the problem that *in utero* infection of the heart regained its primacy as the cause of EFE.

Evidence supporting the infectious etiology of EFE has come from several observations. Hutchins and Vie[3] reported on a group of 64 children in whom 41 had coexisting interstitial (probably viral) myocarditis and idiopathic EFE. These authors noted that with longer survival times the myocarditis subsided while the fibroelastosis increased in severity. A more direct clinical association between viral infection and EFE has been documented in cases of post natal viral myocarditis attributed to mumps, poliovirus type 2[4] and coxsackie B virus[4,5] in which the development of EFE occurred following a variable time period.

Experimental evidence relating viral infection



Fig 7 Two markedly hypertrophied and bizarre mitochondria (M and M) are observed in this myocardial cell Mitochondrial cristae are disorganized Th re appears to be partial fu ion of the enlarged mitochondria *at the arrow* The myocardial nucleus contains viral like particles (V) which are seen better in *Fig 11* (Original magnification ×8 000)

cellular vacuolization The most striking abnormality observed was the presence of intramyocardial vessels completely occluded by intimal proliferation Although occasional vascular abnormalities have been described in EFE occlusive lesions are rare Numerous studies have documented the propensity of several cardiotrophic viruses to infect endothelium however the role of vascular occlusion in the development of myocardial damage and EFE remains speculative Finally the fact that myofiber degeneration and vascular endothelial proliferation were found in skeletal muscle supports our contention that the EFE resulted from infection with virus It is unlikely that abnormal mechanical or hemodynamic forces could have produced the extracardiac lesions

Ultrastructurally hypertrophied cells with irregular nuclei and increased numbers of mitochondria with bizarre and giant forms were observed Numerous intracellular double membrane delimited vacuoles containing cytoplasmic components were frequently noted These vacuoles have recently been described in vascular smooth muscle cells by Joris and Majno These authors provide evidence that the vacuoles represent cell to cell herniae with the protrusion of one cellular plasma membrane into an invaginated adjacent cell producing the double membrane lined space Joris and Majno propose that these vacuoles arise as a result of pathological wall tension or spasm in vessels In the heart these vacuoles are probably indicative of abnormalities of contraction resulting from the endocardial sclerosis and interstitial fibrosis associated with cellular hypertrophy

Myofiber degeneration consisted of focal myofibrillolysis and severe cytoplasmic disruption These features were not invariably associated with nuclear or cytoplasmic viral like material Occasional aggregates of electron dense particles were noted in degenerated cells however they most probably were ribosomal particles

The striking proliferation of endothelial cells within capillary and arteriolar lumens extended the light microscopic observation of a similar process occurring in larger vessels Occasional endothelial cells had associated intranuclear viral like particles As an indication of cellular degeneration many of these small vessels were

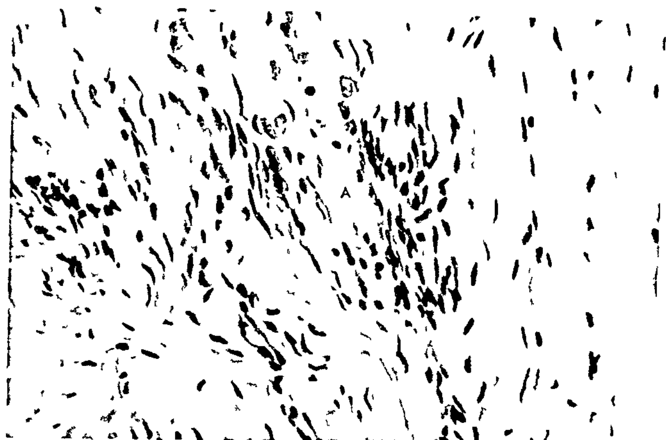


Fig 5 This section of skeletal muscle is infiltrated by *darkly stained inflammatory cells which are also present* within the wall of a distorted artery (*A*) The vascular lumen is obliterated by vacuolated cells identical to those seen in the myocardial vessels (Hematoxylin eosin stain original magnification ×100)



Fig 6 This small interstitial blood vessel is composed of three endothelial cells (*F*) The vessel lumen (*L*) is almost entirely *obliterated* by *proliferated* endothelial cytoplasmic projections (*P*) Small electron dense particles are present within the projection the endothelial cytoplasm and focally in the extra cellular space (*arrow*) Reduplicated basement membrane (*BM*) and cytoplasmic fragments (*CF*) surround the vessel (Original *magnification* ×20 000)



Fig 10 This myocardial cell nucleus contains two aggregated groups of viral like particles (V) Individual non aggregated particles are also present (arrows) The difference in structure and electron density between the viral like particles and the nuclear chromatin and nucleolus can be clearly seen (Original magnification ×37 000)

surrounded by cytoplasmic debris within the interstitium Viral like particles were occasionally observed in these structures

We interpret the aggregates of nuclear particles observed in endothelial and myocardial cells as probably of viral origin Their size and morphology are suggestive of coxsackie virus as well as being similar to the particles described in round heart disease of turkeys [6] Their presence in or near degenerating myocardial cells and hyperplastic endothelium is support for their relationship to the development of EFE in this case Of course it may always be argued that they are the result of a secondary viral infection of an already diseased myocardium and this cannot be easily refuted On the other hand their similarity to coxsackie virus which is known to be clinically associated with EFE [5] suggests a primary relationship

Finally we may speculate on the pathogenesis of EFF in this case and in general If in fact the described particles represent viral related material how do they result in fibroelastosis of the endocardium? If the virus has an affinity for cardiac endothelium it may directly infect the endocardium producing damage and subsequent healing by proliferation of collagen and elastic tissue Alternatively obliteration of multiple vascular channels may lead to scarring of the endocardium as a secondary phenomenon In this regard it may be pertinent that experimental ablation of cardiac lymphatic vessels may produce EFE [11] Although cardiac lymphatics were not clearly involved in experimental mumps induced EFE [8] we could not rule out the possibility that some of the occluded vessels in our case represented lymphatics

Diverse and unrelated cardiac conditions have been associated with EFE These include congenital heart disease [2] myocardial infarction [1] Hurler s syndrome and cardiac glycogenosis Congenital heart disease is frequently the result of *in utero* viral infection [3] and microvascular alterations may be a prominent feature in the myocardium [9] In the other conditions which are clearly non viral in origin vascular abnormalities are obvious in myocardial infarction but they are also present in Hurler s syndrome[1] and Pompe s disease [3] Thus although speculative it is conceivable that intramyocardial occlusive vas



Fig 8 This large intracellular myocardial vacuole contains flocculent and electron dense granular material a degenerated mitochondrion (*M*) and membranous structures The double membrane surrounding the vacuole can be seen *at the arrows* suggesting that the vacuole represents an intracellular hernia (Original magnification ×36 000)



Fig 9 There is severe degeneration of the myocardial cell in the lower portion of the field with similar but less severe changes noted in the cell on the right There is absence or dissolution of myofilaments and complete disorganization of an intercalated disk (*ID*) Membranous material and electron-dense granular particles (*arrows*) are present beneath the still intact sarcolemma The interstitium contains collagen fibers (*C*) (Original magnification ×9 500)



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Fig 11 A high magnification view of the nucleus seen in *Fig 7* demonstrates a loosely aggregated group of viral like particles (*V*) Several of the individual particles (*arrows*) appear to be compo ed of an outer shell and a small central electron dense core (Original magnification ×40 000)

cular disease represents a common denominator for the development of EFE In the future known cases of primary EFE should be studied with particular attention to the myocardial small vessels Additionally electron microscopy and immunologic techniques should be employed to confirm the presence of viral material

Summary

Although clinical immunologic and experimental evidence exists implicating *in utero* viral infection of the myocardium in the development of primary endocardial fibroelastosis the infectious etiology of this condition remains somewhat controversial To date specific features of viral myocarditis and morphological demonstration of viral particles have not been described in EFE The present case is the first in which extensive light microscopic and ultrastructural analysis of the myocardium revealed abnormalities consistent with a primary viral myocarditis associated with typical EFE These alterations consisted of chronic myocardial inflammation extensive interstitial fibrosis severe degenerative changes in myocardial cells and a marked proliferation of endothelial cells in large and small intramyocardial vessels leading to vascular occlusions In support of the infectious etiology of this disease similar features were noted in skeletal muscle Most interestingly viral like particles were observed in many myocardial and endothelial nuclei Although we are not absolutely certain of the viral nature of these particles their appearance suggests viral associated material We propose that the presence of these particles in this case in association with the other morphological alterations is support for the viral etiology of EFE The prominent vascular occlusion observed in the myocardium may be an important clue to the pathogenesis of fibroelastosis as either a primary or secondary disease

I would like to express my appreciation to Dr Luis Biempica for his extremely helpful comments and suggestions to Mrs Stella Biempica for her fine technical assistance and to Ms Constance Verutes for her excellent secretarial aid in preparing this manuscript

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Fig 1 Cross section of left anterior descending coronary artery with Teflon felt embolus lodged at a point of branching ~5 cm from the ostium *(black arrows)* (Embolus measures 0 4 cm in greatest diameter) (Original magnification approximately ×2)

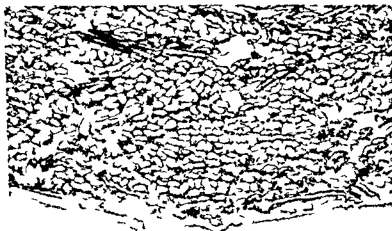


Fig 2 Photomicrograph of the Teflon felt embolus within the coronary artery (*Hematoxylin* and eosin original magnification ×60)

Autopsy findings The heart weighed 580 grams with marked left ventricular hypertrophy The prosthetic valve was in place There were no thrombi on the surface of the disc or on the cage of the prosthesis The coronary arteries were cross sectioned at 3 mm intervals There was a complete occlusion of left anterior descending coronary artery by an embolus of fibrillar foreign material 5 5 cm from the left coronary ostium (Fig 1) Microscopically the embolus was composed of relatively uniform fibers, oriented along the long axis of the vessel (Fig 2) The embolic material was histologically identical to fibers of Teflon taken from a piece of Teflon felt used to buttress sutures on the Bjork Shiley valve (Fig 3) The remaining coronary arteries had moderate atherosclerosis with no significant luminal narrowing

The myocardium was cut transversely at 1 cm intervals and the slices were stained with nitro blue tetrazolium (NBT) (Fig 4) This revealed a large non-staining area in the anterior wall and anterior septum indicating recent myocardial infarct Microscopically there was extensive eosinophilia of the fibers disruption of the cross striations loss of nuclei and margination of polymorphonuclear leukocytes in capillaries near the necrotic muscle These findings confirmed the presence of a large anterior myocardial infarction less than 24 hours old Both the age and distribution of the infarct correspond with an occlusive embolus to the left anterior descending coronary artery

All sections of the myocardium contained small patches of granulation tissue with loss of muscle fibers and a predomi

Teflon felt embolism of coronary arteries after cardiac surgery A case report

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Teflon felt and mattress sutures buttressed with a small pledget of Dacron or Teflon cloth are commonly used in cardiac surgery In cardiac valve replacement they are sometimes used to attach the valve prosthesis to the valvular ring and to avoid tearing of the sutures through the annulus In the case reported here, a piece of Teflon embolized to the left anterior descending coronary artery resulting in complete occlusion and extensive acute myocardial infarction 10 days after the insertion of a Bjork Shiley aortic valve prosthesis Only two previous documented cases of Teflon embolism of coronary arteries causing myocardial necrosis have been reported[1] These cases were characterized by multiple embolization of small intramural coronary arteries and arterioles after replacement of individual valve cusps by cusps made of Teflon This case is unique in that Teflon embolism caused occlusion of an extramural coronary artery resulting in extensive acute myocardial infarction in the occluded artery distribution This unusual complication has been not previously described with the use of the Bjork Shiley tilting disc valve

Case report

M G was a 48 year old female with a known heart murmur for 18 years asymptomatic until 2½ years before admission when she developed substernal pressure sensation with exertion progressive shortness of breath ankle edema and nocturnal dyspnea She was known to have thalassemia minor and adult onset diabetes mellitus A left nephrectomy had been done seven years previously for cystic disease and an enlarged liver by biopsy was found to have micronodular cirrhosis and fatty metamorphosis She had been treated with daily digoxin and diuretics Blood pressure was 110/60 mm Hg pulse was regular and she was in no preoperative distress The heart was clinically enlarged there was a III/VI holosystolic murmur at the cardiac base radiating to the carotids and a II/VI blowing diastolic murmur present at the low left sternal border and apex of the heart There was mild hepatosplenomegaly An electrocardiogram showed a sinus rhythm and nonspecific ST and T wave abnormalities chest x ray revealed slight cardiomegaly Cardiac catheterization showed calcific aortic stenosis and moderate aortic insufficiency The left ventricular end-diastolic pressure was 18 mm Hg with a cardiac index of 3 02 L/min /M[2] The coronaries were angiographically normal

The operation was done with moderate hypothermia and continuous coronary perfusion with a beating heart The aortic valve had three definite well suspended leaflets with thickened rolled edges commissural fusion and calcium deposits The valve was totally excised removing a portion of the ring beneath the left coronary sinus This was repaired with two mattress sutures buttressed with Teflon felt A No 23 Bjork Shiley aortic valve was placed with interrupted mattress sutures each buttressed with Teflon felt placing these from the ventricular side of the ring through the ring and the sewing ring of the prosthesis

The postoperative course initially was uncomplicated She was anticoagulated and ready for discharge on the tenth postoperative day when she developed severe crushing chest pain tachycardia and mild hypotension ECG s revealed acute changes of an anterolateral myocardial infarction The hypotension worsened ventricular arrhythmias occurred and in spite of pharmacologic support intraaortic balloon counter pulsation and respiratory support she died within 24 hours of the onset of her chest pain It was suspected clinically that in spite of her anticoagulation with Coumadin which had been in the therapeutic range since her seventh postoperative day she had suffered a prosthetic thrombus with an embolus to the left coronary artery

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Received for publication Oct. 21 1977
Accepted for publication Nov 1 1977

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embolism of coronary arteries resulting in myocardial necrosis[1,2] These were late complications following individual aortic leaflet replacement by Teflon prosthetic leaflets The emboli involved multiple small intramural coronary arteries

Coronary embolism of Teflon material has not been previously reported following the use of Teflon felt buttressed sutures for placement of a Bjork Shiley tilting disc valve Henze and associates reviewed the cause of death and major pathology of the patients following 161 aortic valve replacements with the Bjork Shiley tilting disc valve Eight of the 161 patients died within 30 days of operation (hospital mortality rate 5 per cent) and 12 patients died after 30 days (7 per cent) Myocardial failure (nine cases) was the prominent cause of death in this series They encountered no thromboembolic complications in survivors with anticoagulation treatment after insertion of the Bjork Shiley valve in the aortic position In the case reported here a piece of Teflon felt embolized to the left anterior descending coronary artery resulting in total occlusion and extensive acute myocardial infarction in the distribution of the occluded artery The source of the embolus was the Teflon felt used to buttress sutures used to hold the valve These Teflon pledgets lie on the ventricular side in the outflow stream of the left ventricle The reason for the detachment of a fragment of Teflon felt in this case is unexplained The clinical and pathologic findings clearly established that the embolism of the occluded artery occurred on the tenth postoperative day and not at the time of surgery This case demonstrates that the use of Teflon or similar synthetic material in cardiac valve replacement even with the improved valve prosthesis should be regarded as a potential embolic source and a rare cause of coronary occlusion

Summary

A case is presented of fatal coronary embolism of Teflon felt used to buttress sutures in the placement of a Bjork Shiley aortic valve prosthesis The embolism occurred on the tenth postoperative day lodging in the left anterior descending branch of the left coronary artery 5 5 cm from the ostium causing a large anterior myocardial infarct The patient died in less than 24 hours following the infarct A review of the literature indicates that this is the first reported case of clinically significant embolism of Teflon felt used in the placement of a Bjork Shiley aortic valve

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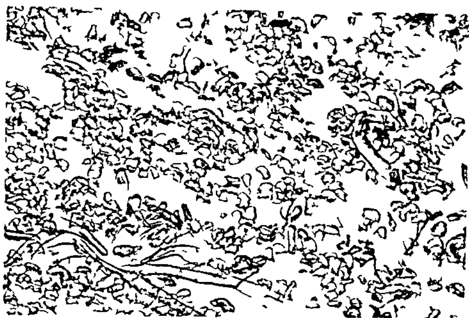


Fig 3 Photomicrograph of a Teflon felt pledget taken from the patient's aortic valve prosthesis (Hematoxylin and eosin original magnification ×60)



Fig 4 Gross photograph of slices of ventricular myocardium stained with nitro blue tetrazolium (NBT) the pale non staining area (*between arrows*) is the recent myocardial infarct involving the anterior wall of the left ventricle and anterior portion of the septum

nantly mononuclear infiltrate These tiny infarcts were approximately two weeks old corresponding to the time of open heart surgery Multiple foci of cardiac ischemia have been reported in the literature and have been ascribed to open heart surgery

Other findings included micronodular cirrhosis of the liver compensatory hypertrophy of the right kidney with mild arteriolar nephrosclerosis fatty infiltration of the pancreas and chronic non specific thyroiditis

Discussion

Coronary embolism is an infrequent cause of myocardial infarction and is listed in standard textbooks as a rare cause of coronary artery disease Coronary emboli most frequently occlude the left coronary artery particularly its left anterior descending branch Wenger and Bauer[7] found 11 cases of coronary artery embolism in 17 469 consecutive autopsy cases at Mt Sinai Hospital, New York for a general necropsy incidence of 0 06 per cent Despite anticoagulation therapy, thrombosis of the prosthetic valve after cardiac valve replacement is still an important complication and a potential source of systemic or pulmonary embolism Cases of coronary embolism and myocardial infarction from thrombus following insertion of a Starr Edwards prosthesis have been reported [8] Also embolic material such as calcium suture and foreign bodies have been described in small intramural coronary arteries as incidental autopsy findings after open heart surgery [10] Two documented cases have been found in the literature of Teflon

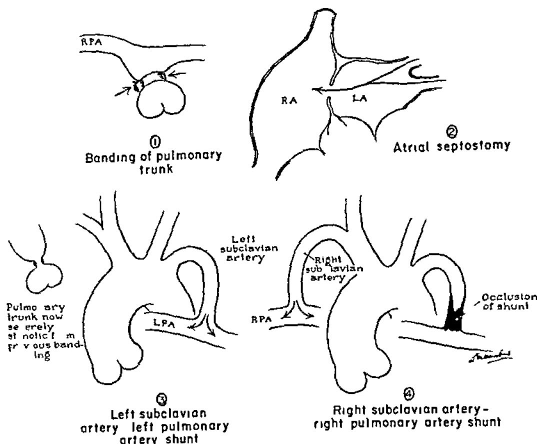


Fig 1 Diagram illustrating the operative procedures carried out in the child described *RPA* and *LPA* = right and left main pulmonary arteries *RA* = right atrium *LA* = left atrium

Table I Hemodynamic data in patient T H

Age at study (months)	*3*		*10*		*19*		*60*		*84*	
	P	*O*	*P*	*O*	*P*	*O*	*P*	*O*	*P*	*O*
Superior vena cava	–	–	–	–	3	70	5	33	–	–
Right atrial mean	6	47	3	50	3	70	5	33	–	–
Right ventricle	85/10	94	110	–	110/10	86	125/5	44	80/50	60
Pulmonary artery	–	–	–	–	–	–	–	–	–	–
Pulmonary vein	–	97	–	–	8	97	–	–	–	–
Left atrial mean	12	94	9	95	8	97	–	–	–	–
Left ventricle	85/9	93	–	–	–	–	–	–	–	–
Aorta	–	–	150/90	80	110/60	86	125/78	44	120/40	60
qP qS					1 7 1		1 5 4			

Abbreviation P = pressure in mm. Hg O = oxygen saturation in per cent qP qS = pulmonic to-systemic flow rat

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Dr Roberts Doctor Chandra could you summarize the finding at necropsy?

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Clinical pathologic conference

Complex congenital heart disease
A multiplicity of therapeutic options

Lewis P Scott, M D *
Roma S Chandra, M D **
William C Roberts, M D ***
Washington D C and Bethesda Md

DR ROBERTS In this report, a boy with cyanotic congenital cardiac disease will be presented and problems manifested in him will be discussed Dr Scott will describe his patient

DR SCOTT T H (*CHNMC No 299 3972*) a 7 year old black boy who died in December 1976 was noted to have cyanosis and a precordial murmur at 2 weeks of age Shortly thereafter signs of congestive heart failure developed At 3 months of age cardiac catheterization (Table I) provided a diagnosis of transposition of the great arteries with single ventricle The pulmonary trunk was banded at this time with reduction of the systolic pressure in this artery from 85 to 45 mm Hg (Fig 1) Despite this procedure, however the child failed to thrive and cyanosis increased Inadequate intracardiac mixing of blood was considered the reason and accordingly a Rashkind atrial septostomy was performed at 9 months of age (Fig 1) The transatrial pressure difference was reduced by this procedure from 9 to 3 mm Hg

Because of persistent growth failure and cyanosis catheterization was repeated at 19 months of age (Table I) Subsequently, growth continued to be slow, exercise tolerance poor and polycythemia increased Still another catheterization at 5 years of age disclosed severe reduction in systemic arterial saturation compared to previous studies (Table I) Although the pulmonary trunk was not entered by the catheter, the pressure in the distal pulmonary artery by clinical examination was believed to be low Accordingly a left subclavian to pulmonary arterial anastomosis was performed (Fig 1) The distal portion of this left subclavian artery, however thrombosed almost immediately and then a right subclavian to right pulmonary arterial anastomosis was done (Fig 1) This second shunt remained open as evidenced by the development of a continuous murmur over the precordium Nevertheless cyanosis persisted and polycythemia worsened Multiple hospitalizations for phlebotomies followed During the next several months fever periodically appeared and a diastolic basal precordial murmur suggesting aortic regurgitation developed Blood cultures were always negative and the cause of the recurring fever was never determined

The last hospitalization was at age 7 years for another cardiac catheterization Its purpose was to again try to measure the pulmonary arterial pressure and resistance The right subclavian artery was entered retrogradely from the femoral artery The catheter was advanced into the right

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Received for publication Nov 15 1977

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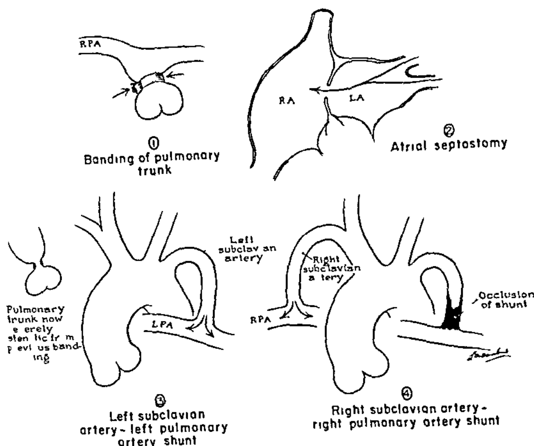


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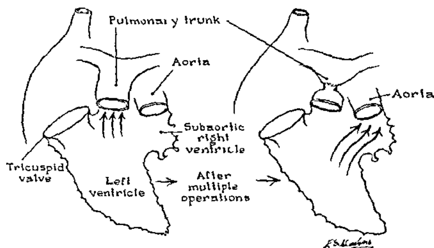


Fig 3 Diagram showing the change in intracardiac blood flow which occurred before any cardiac operation *(left)* and after complete occlusion of the pulmonary trunk by the banding procedure *(right)*

DR ROBERTS As I understand it Dr Scott you did the last cardiac catheterization on this child to see if the pulmonary arterial pressure was elevated and indeed you did find that the pressure in this artery was quite elevated Yet at necropsy the pulmonary arteries in both lungs were devoid of changes suggestive of pulmonary hypertension Indeed many of the pulmonary arteries showed changes suggestive of pulmonary hypotension rather than hypertension *What is your explanation for the finding of pulmonary hypertension in this child at the final catheterization?*

DR SCOTT It is apparent from the necropsy findings that there was no pulmonary blood flow entering the lesser circuit from the right ventricular outflow tract The only perfusion of the pulmonary circuit was through the right subclavian anastomosis and bronchial vessels With the catheter in the right subclavian artery pulmonary blood flow apparently was severely decreased In all probability near occlusion of the right subclavian artery by the catheter produced acute hypoxia which caused severe spastic constriction of the smaller pulmonary arteries and arterioles resulting in severe elevation of the pulmonary arterial pressure

DR ROBERTS Dr Scott I believe you were quite concerned with the increasing polycythemia in this child during his last several years and consequently several therapeutic phlebotomies were performed *What are your indications today for doing phlebotomy in individuals with cyanotic congenital heart disease?*

DR SCOTT With rising hematocrit the resulting increased viscosity in blood can induce intravascular thrombosis in both pulmonary and systemic vessels When a child develops hematocrit values above 65 per cent we usually recommend phlebotomy By reducing viscosity the tendency for intravascular thrombosis is reduced and in addition the stroke work of the ventricle is reduced and consequently cardiac output improves

DR ROBERTS Dr Scott suppose that in this patient the banding procedure had been ideal i e the pulmonary arterial pressure distal to the band was normal and that growth and development progressed well Had that occurred what would have been your subsequent plan for this child?

DR SCOTT There are several options open to the cardiologist and cardiovascular surgeon today None of these options however are truly optimal and I would not recommend any of them as long as the patient was relatively asymptomatic and grew normally In the event that deterioration began a total corrective operation wherein a ventricular septum would be created assuming of course that two well developed atrioventricular valves existed should be considered At the same time one would have to remove the band on the pulmonary trunk A second option would be a modified Fontan operation the tricuspid valve orifice would be closed and a conduit connected from the right atrial appendage to the distal pulmonary artery To carry out such a procedure pulmonary vascular resistance would have to be low and the function of the single ventricle would have to be excellent Before performing the Fontan operation the right pulmonary artery

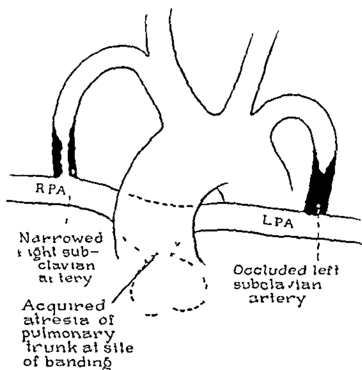


Fig 2 Diagram summarizing the operative procedures carried out on the pulmonary trunk and main right *(RPA)* and left *(LPA)* pulmonary arteries and their consequences

atrioventricular valves entered the large ventricle which anatomically was left ventricular in type The coronary arteries were mirror image of normal (Fig 4) On the ventricular aspects of each of the three cusps of the aortic valve small bumps composed mainly of fibrous tissue but also some calcific deposits, were present The pulmonary trunk was totally occluded by fibrous tissue at the site of the banding The distal portion of the left subclavian artery also was occluded by fibrous tissue (resulting from organization of thrombus) just proximal to its anastomosis to the left main pulmonary artery The right subclavian artery was wide open Histologic examination of sections from both lungs showed entirely normal pulmonary arteries and arterioles

Dr Roberts This child s course and therapeutic interventions raise questions regarding management of patients with cyanotic congenital heart disease secondary to complex malformations This boy s early course was characterized by evidence of *excessive* pulmonary blood flow and consequently the pulmonary trunk was banded His *course* thereafter was characterized by evidence of *inadequate* pulmonary blood flow and *consequently* attempts (Blalock Taussig anastomoses) *were made to* increase pulmonary blood flow Dr Scott I am aware that the banding of the pulmonary trunk in this child was done before the child presented to you If however, we could start again ' in this child *what would be the initial operative procedure you would recommend and why?*

Dr Scott Our major concern in a child presenting with pulmonary overflow associated with single ventricle and transposition is to control congestive heart failure and to prevent growth failure the usual major presenting problems in this situation Over the long run of course prevention of the development of pulmonary vascular disease is essential Consequently banding of the pulmonary trunk remains an excellent procedure to reduce congestive cardiac failure and prevent growth failure In the presence of moderately elevated left atrial pressures however, we would perform atrial septostomy at the time of the initial cardiac catheterization There appears to be a relationship between the elevation of the left atrial pressure and the rapidity with which the pulmonary vascular disease develops

Dr Roberts Dr Scott, *why does pulmonary vascular disease develop so rapidly* as a rule in the child with single ventricle and transposed great arteries?

Dr Scott There are multiple factors The high pressure and flow through the pulmonary arteries are certainly major contributors to the induction of these vascular changes Just as important however are the left atrial pressure and the presence of hypoxemic blood in the bronchial circulation

Dr Roberts The banding of the pulmonary trunk in this child diminished the pulmonary arterial systolic pressure measured at the time of operation from approximately 85 to 45 mm Hg Yet by the time necropsy was performed nearly six years later the pulmonary trunk was totally obstructed at the site of the band Dr Scott do you have an *explanation for this acquired atresia of the pulmonary trunk at the site of banding?*

Dr Scott I have never observed a patient previously in whom banding of the pulmonary trunk progressed to total occlusion of its *lumen* It is recognized that total obstruction to right ventricular outflow may occur in a patient with tetralogy of Fallot who has had a systemic to pulmonary arterial shunt created operatively ' What caused the especially severe fibrosis around the band in the present patient with eventual total occlusion of the pulmonary trunk is unclear

Coagulation for cardiologists

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Vascular patency depends upon the balance between at least six subtly interrelated systems each of which in itself is exceedingly complex These include the endothelium and its subjacent structures the platelets the coagulation and fibrinolytic systems the inhibitors of these latter systems and the flow characteristics of blood within the circulation Alterations of the rather delicate balance among these hemostatic systems can result in serious hemorrhage or major thromboembolism In the discussion that follows the focus will be directed to the issue of thrombosis and its management

Basic aspects of hemostasis as they relate to thrombosis

The endothelium and the platelet Intact endothelial cells prevent platelet aggregation by at least two mechanisms They act as a physical barrier between thrombocytes and subendothelial structures such as collagen which can initiate platelet aggregation they also have the capacity to synthesize a prostaglandin prostacylin (PGI_2) that is a potent inhibitor of platelet aggregation

Damage or disruption of the integrity of the endothelial cell by a variety of agents can initiate thrombosis a phenomenon that may potentiate the earliest phase of atherosclerosis Though platelets do not attach to intact endothelial cells they do adhere to exposed collagen when the endothelial barrier is disrupted whereupon the platelet undergoes a series of changes termed the release reaction Included in this reaction is the release from platelet storage pools of ADP which causes additional reversible thrombocyte aggregation and further release of ADP thus sustaining the initial platelet aggregation[1] that is still reversible Platelet aggregation moreover results in the release of phospholipid (platelet factor 3) an element essential to the coagulation process

The exposed subendothelial structures in addition to their effect on platelet function also activate the clotting sequence leading to the production of thrombin a serine protease that forms fibrin from fibrinogen Thrombin can also induce irreversible platelet aggregation by initiating the synthesis of thromboxane A2[10] as well as platelet actomyosin contraction[11] which along with the production of fibrin consolidates the platelet plug This description of platelet function has relevance to the prevention of arterial thrombosis

The coagulation system The coagulation system has been depicted as a series of proenzyme to activated enzyme transformations [*] that involve biochemical amplification Such a sequence allows a relatively few molecules of a clot initiator to produce a biochemically explosive amount of thrombin in a short period of time

Blood clotting can be precipitated either by contact activation (the intrinsic system Fig 1) or by traumatic release of tissue thromboplastin (the extrinsic system Fig 1) The two systems converge at factor X and continue along a common pathway to fibrin formation

In the intrinsic system clotting is initiated by the adsorption of factor XII onto a foreign surface such as collagen[14] Both kallikrein and

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Supported by N t onal Heart Lung a d Blood Institute Grant No 2 R01 HL 18333 N t nal Inst tutes of H lth Dept of Health, Ed at on, nd Welf re

Rece ved f r public t on Apr 24 1978.

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* The relat onsh ps of the various cl tting factors can be f llowed by referri g to Fig 1

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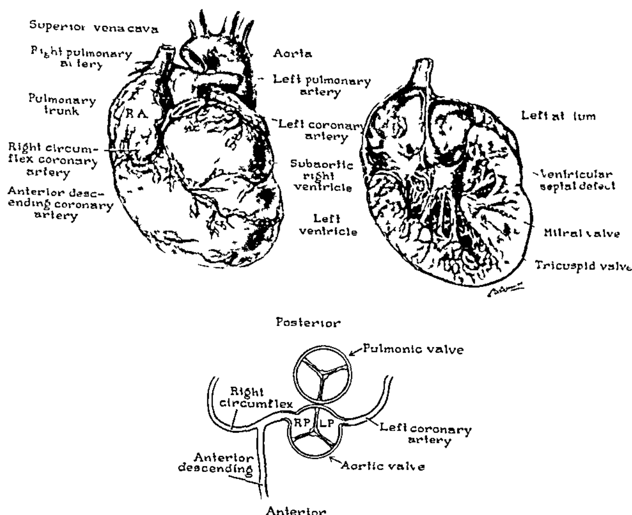


Fig 4 Drawings showing the various intrathoracic cardiovascular malformations observed in the patient described The aorta arises anteriorly and from a small subaortic chamber The large ventricle located mainly on the right side has the interior lining of an anatomic left ventricle The coronary arteries are mirror image of normal

should be anastomosed to the superior vena cava Had the Blalock Taussig anastomoses already been performed a third operative option would be to reanastomose or close off the anastomoses and perform a Waterston type shunt between ascending aorta and pulmonary artery

Dr Roberts Dr Scott, I understand that a basal diastolic blowing murmur was audible in this child during the last few months of life What was your *explanation for this murmur?*

Dr Scott I initially thought that the diastolic murmur was produced by insufficiency of the pulmonic valve As the aortic diastolic pressure began to fall however it was apparent that this murmur was due to runoff through the aortic valve On several occasions this patient had fever for rather protracted periods Multiple blood cultures were obtained, but all *were negative* Short term courses of antibiotics for upper respiratory tract and ear infections probably allowed cure of the probable associated infective endocarditis which caused the aortic regurgitation

Dr Roberts At necropsy there were lesions on each of the three aortic valve cusps which were consistent with healed infective endocarditis[2] Occurrence of infective endocarditis in children is quite unusual Those with endocarditis in childhood nearly always have underlying congenital heart disease but, in contrast to this child it is usually of the acyanotic variety[3]

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Fundamentals of clinical cardiology

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Vascular patency depends upon the balance between at least six subtly interrelated systems each of which in itself *is exceedingly complex* These include the endothelium and its subjacent structures the platelets the coagulation and fibrinolytic systems the inhibitors of these latter systems and the flow characteristics of blood within the circulation Alterations of the rather delicate balance among these hemostatic systems can result in serious hemorrhage or major thromboembolism In the discussion that follows the focus will be directed to the issue of thrombosis and its management

Basic aspects of hemostasis as they relate to *thrombosis*

The endothelium and the platelet Intact endothelial cells prevent platelet aggregation by at least two mechanisms They act as a physical barrier between thrombocytes and subendothelial structures such as collagen which can initiate platelet aggregation[1] they also have the capacity to synthesize a prostaglandin prostacylin (PGI) that is a potent inhibitor of platelet aggregation

Damage or disruption of the integrity of the endothelial cell by a variety of agents can initiate thrombosis a phenomenon that may potentiate the earliest phase of atherosclerosis Though platelets do not attach to intact endothelial cells they do adhere to exposed collagen when the endothelial barrier is disrupted whereupon the platelet undergoes a series of changes termed the release reaction Included in this reaction is the *release from platelet storage pools of* ADP which causes additional reversible thrombocyte aggregation and further release of ADP thus sustaining the initial platelet aggregation ' that is still reversible Platelet aggregation moreover results in the release of phospholipid (platelet factor 3) an element essential to the coagulation process*

The exposed subendothelial structures in addition to their effect on platelet function also activate the clotting sequence leading to the production of thrombin a serine protease that forms fibrin from fibrinogen Thrombin can also induce irreversible platelet aggregation by initiating the synthesis of thromboxane A2[10] as well as platelet actomyosin contraction[11] which along with the production of fibrin consolidates the platelet plug This description of platelet function has relevance to the prevention of arterial thrombosis

The coagulation system The coagulation system has been depicted as a series of proenzyme to activated enzyme transformations [13] that involve biochemical amplification[12] Such a sequence allows a relatively few molecules of a clot initiator to produce a biochemically explosive amount of thrombin in a short period of time

Blood clotting can be precipitated either by contact activation (the intrinsic system Fig 1) or by traumatic release of tissue thromboplastin (the extrinsic system Fig 1) The two systems converge at factor X and continue along a common pathway to fibrin formation

In the intrinsic system clotting is initiated by the adsorption of factor XII onto a foreign surface such as collagen Both kallikrein and

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S pported by Nat o l H art L g and Blood In t tute Grant No 2 R01 HL 18333, N tio al I stitutes f He lth Dept of Health Edu ation and W lf re

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*The rel t hips of the various cl tting factors can be followed by referring to Fig 1

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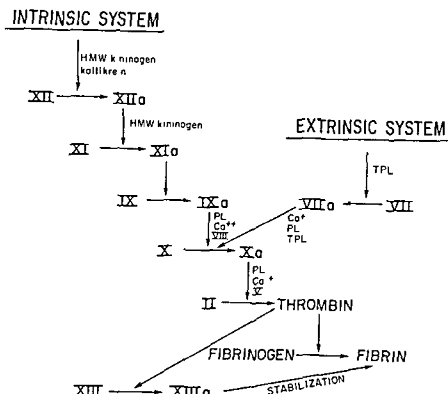


Fig 1 Relationships of the various clotting factors Abbreviations *HMW kininogen* = high molecular weight kininogen *PL* = phospholipid *TPL* = tissue thromboplastin The subscript *a* indicates that the protein has been activated Vitamin K dependent zymogens are Factors VII IX X and II (Prothrombin) XIIa XIa IXa Xa and thrombin can be inhibited by antithrombin III and the rate of this inhibition is accelerated by heparin Factors V and VIII attain maximum cofactor activity after activation by thrombin

high molecular weight kininogen are required for the rapid surface activation of factor XII to an activated serine protease XIIa [15 17] In addition high molecular weight kininogen increases the reactivity of XIIa in the conversion of factor XI to its activated form XIa

XIa itself a serine protease converts factor IX to an activated serine protease IXa Then factors VIII and IXa form a complex which results in the activation of factor X [18] Both phospholipid, made available by aggregated platelets, and Ca are essential to activate factor X at a maximum rate [19] Subsequently the serine protease Xa, in the presence of factor V Ca and phospholipid converts prothrombin to thrombin [0 21]

The extrinsic system is triggered by the release of tissue thromboplastin a protein-phospholipid mixture that activates factor VII [3] Together they serve as cofactors with Ca for the activation of factor X Once Xa is formed thrombin production proceeds as described above

Thrombin is the final serine protease formed in the coagulation sequence It cleaves fibrinogen to fibrin induces platelet aggregation and activates factor XIII to XIIIa, a transamidase that covalently links fibrin monomers into a fibrin mesh in the presence of Ca [+] Thrombin is also capable of activating factors VIII [1] and V [6] from either inactive or partially active forms to highly reactive molecules Thus, for the coagulation system to function at its maximum potential minute amounts of thrombin are required

In general coagulation can be viewed as a series of zymogen activations to serine proteases that are enhanced by Ca , phospholipids and regulatory proteins The sequential activation contributes to an amplification of the thrombotic stimulus [12] so that a sufficient amount of thrombin is produced to form a stable thrombus These biochemical reactions also have therapeutic implications

The fibrinolytic system Plasminogen a proenzyme normally present in plasma can be converted to the active enzyme plasmin This conversion is induced by an activator present in most body tissues including endothelial cells The release of this activator is mediated by either XIIa thrombin or hypoxia Plasmin a serine protease enzymatically cleaves fibrin into soluble fragments Besides degrading fibrin plasmin can also degrade fibrinogen prothrombin and factors

VIII and V Thus it might appear that the use of a fibrinolytic agent could be a double edged sword removing thrombi once their physiological role in hemostasis had been completed yet causing hemorrhage because of the degradation of clotting proteins other than fibrin that are essential to the integrity of the vascular tree—a dilemma that is amenable to solution but posed in different ways and to different degrees by all pharmacological agents that affect the hemostatic balance

Inhibitory systems Normal human plasma contains several serine protease inhibitors capable of neutralizing activated clotting species The only inhibitor in this group whose concentration and activity[3] have been correlated with a thrombotic disorder is antithrombin III This α_2 globulin with a molecular weight of 63 000 has a major role in maintaining the fluidity of the blood[3] In purified systems antithrombin III inhibits thrombin and Xa At significantly slower reaction rates this α_2 globulin also inhibits XIIa XIa and IXa[1] Antithrombin III forms an undissociable complex with activated clotting factors in which one molecule of antithrombin III forms a covalent ester linkage at the active site of the protease

Although antithrombin III will also inhibit the serine protease plasmin other inhibitors such as α_2 macroglobulin[8] and a specific plasmin inhibitor α plasmin inhibitor are more effective in preventing the action of circulating plasmin Since plasmin is readily blocked in the circulation only plasmin produced or localized within the thrombus facilitates clot dissolution Several mechanisms whereby this may occur have been postulated

These inhibitors also have important therapeutic roles

Blood flow Although the relationship between various parameters of blood flow and thrombosis are still being unravelled there are some generalizations that can be provided Retarded blood flow while it cannot cause intravascular coagulation does facilitate the thrombotic process once it is initiated Stasis can occur not only in veins but also in arteries at bends and bifurcations If a platelet or other thrombus is effective in halting or nearly halting the flow of blood such static movement will facilitate the thrombotic process by mechanically protecting it from being washed away by fluid blood From fluid mechanics it can be proposed that in areas of retarded flow thrombus evolution would be favored in the plasma phase within the static red cell network because thrombin and other serine proteases would be protected from dilution to subcritical concentrations from inflow of plasma inhibitors and from clearance of proteases by the liver whereas nascent fibrin would be protected from premature dispersion It is formulations such as this that justify efforts at least in the peripheral venous circulation where such an approach is feasible to reduce or prevent thrombosis by mechanical devices that accelerate venous blood flow either in place of or in conjunction with antithrombotic agents

The pharmacology of antithrombotic agents

There are presently available several classes of drugs which have been used to inhibit or control thrombosis These include platelet antiaggregants such as aspirin dipyridamole (Persantine) and sulfinpyrazone (Anturane) vitamin K antagonists such as warfarin (Coumadin) antithrombin III protentiators such as heparin plasminogen activators such as streptokinase and urokinase depleters of fibrinogen such as ancrod and the dextrans which have a variety of potentially antithrombotic actions

Platelet antiaggregants

Aspirin This drug has been shown to inhibit prostaglandin synthesis in platelets Aspirin acetylates a protein prostaglandin cyclooxygenase[5] thereby irreversibly inhibiting this enzyme and blocking synthesis of prostaglandin endoperoxides which are potent platelet aggregants Aspirin also partially blocks the production of thromboxane A2 another potent platelet aggregant

On the other hand aspirin also blocks prostaglandin synthesis in endothelial cells One of these endothelial prostaglandins PGI is a potent platelet *anti*aggregant By blocking the synthesis of PGI one may possibly counteract the anticoagulant effect of aspirin on the platelet Whether these two opposite effects can be separated by a proper choice of dose is presently unknown The value of aspirin as an antithrombotic agent may be determined by the results of ongoing trials

As stated previously aspirin inhibition is irreversible accounting for the duration of the effect of this compound on platelet function for the

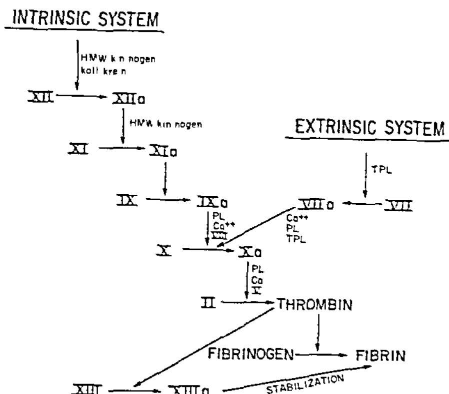


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Dextrans In its original form dextran is a branched polysaccharide of about 200 000 glucose units with a molecular weight of approximately 40 million. The glucose units in the main chain are bound together through 1 6 glucosidic linkages, those in shorter branches through 1 4 linkages. By means of partial hydrolysis and subsequent fractionation native dextran can be converted to polysaccharides of any desired range of molecular weight. In general it is fair to say that clinical complications increase with higher average molecular weight, broader molecular weight distribution, and a more pronounced degree of branching of the molecule. The two most important preparations currently in use are a 70 000 molecular weight preparation with the trade name Macrodex or Dextran 70 and a 40 000 molecular weight compound known as Rheomacrodex or Dextran 40.

Fibrin deposited in the presence of dextran is morphologically different from fibrin in normal clots[7] resulting in a decrease in its mechanical strength and an increase in its porosity.[73] These properties favor both the inability of the fibrin clot to withstand shear stress in flowing blood and the rate at which fibrinolysis can occur. Dextran also decreases platelet aggregability. On the other hand, dextran increases the rate of blood flow which may, particularly in cardiac patients, precipitate pulmonary edema. The drug may also induce allergic reactions.

Venoms Various snake venoms have striking effects on the coagulation and fibrinolytic systems. The venom from the Malayan pit viper contains a protein, ancrod, that is capable of converting plasma fibrinogen to fibrin.[7] However, since factor XIII is not activated, the resulting fibrin cannot form a stabilized precipitate. Accordingly, the unstabilized thrombus can be readily broken up and promptly removed from the circulation. In man, the intravenous administration of ancrod produces a rapid decrease in plasma fibrinogen which results in an hypocoagulable state that can prevent thrombosis but also produces hemorrhage at venipuncture sites as well as easy bruising. Although used abroad, the drug has not yet received FDA approval and consequently is not presently available for clinical use in the United States.

Clinical status of antithrombotic agents

Platelet antiaggregants On the basis of the role of the platelet in hemostasis and the failure of heparin or the coumarin drugs to prevent arterial thrombosis, it is natural that increasing knowledge of the pharmacology of several platelet antiaggregating agents should suggest that these drugs may have important therapeutic implications for the prevention of arterial thrombosis. Most of the studies have been conducted in vitro or in animals, but in recent years some of these agents have been subjected to clinical trials, several of them still ongoing. Thus, although there is little question that the issue of preventing arterial thrombosis with platelet antiaggregants is currently an exciting area of antithrombotic clinical investigation, the published data require that enthusiasm be tempered with patience.

Aspirin There have been several reports on the use of aspirin in patients with *transient* ischemic attacks (TIA). The goals were cessation of subsequent TIA, prevention of stroke (for which TIA is prodromal), and a decrease in *mortality rate* (much of which comes from heart disease rather than from cerebrovascular accidents). These publications consist of case reports, retrospective and prospective trials.

One stimulus for these trials has come from a variety of reports suggesting that aspirin users have a remarkably low incidence of coronary artery disease. In one of these studies[79] the incidence of TIA was significantly reduced, but comparable advantages for stroke and mortality rate were not obtained. In addition, the soundness of the trial design itself has been questioned.[80] Further trials involving aspirin are currently in progress, however, and when they are reported, a more definite answer to the value of aspirin may emerge than is presently available.

As in TIA, the benefit of aspirin in myocardial infarction is still being evaluated in regard to recurrent infarction and mortality rate. Two completed trials showed favorable trends but did not reach statistical significance. Two secondary prevention trials, now in progress, are evaluating the efficacy of aspirin among patients who have recovered from acute myocardial infarction. Their findings are awaited with great interest.

On the other hand, in arteriovenous shunts among patients on hemodialysis[3] and in hemodialyzers,[84] aspirin does appear to have significantly reduced the incidence of thrombosis.

Aspirin in combination with dipyridamole has corrected platelet consumption observed among patients with prosthetic heart valves.[8] The role of aspirin alone on this effect is unknown and

lifetime of the thrombocyte (seven to ten days) Presumably the effect on endothelial cells is also irreversible and would be lost only when new endothelial cells replace the aspirin affected ones

Sulfinpyrazone This drug is a uricosuric agent used in the treatment of gout The compound is a potent competitive inhibitor of platelet prosta glandin synthetase activity[51] However, unlike aspirin the effect is only transient The in vitro effect of this agent is most marked when aggrega *tion is induced by dilute collagen* suspensions[52] The effect of sulfinpyrazone on endothelial pros taglandin synthesis, specifically PGI_2 has not yet *been determined*

Dipyridamole This compound in vitro inhibits ADP induced platelet aggregation [54] as well as *the platelet release reaction*[55] *The drug blocks* platelet cyclic AMP phosphodiestrase activity, thereby inhibiting the conversion of cyclic AMP to AMP[56] The *mechanism* whereby *dipyridamole* inhibits platelet aggregation is still to be deter mined

Heparin Heparin is a glycosaminoglycan wide ly distributed in animal tissues that is chemically heterogeneous and exhibits polydispersion in molecular weight A property of the heparin molecule essential to its anticoagulant activity is the presence of N sulfate groups on the 2 amino 2 deoxy hexose components as well as O sulfate moieties on the L iduronic acid and the amino hexose residues As an illustration of the complex nature of heparin electrofocusing of the com pound has identified 21 components in a single heparin sample

The function of heparin as an anticoagulant is *to accelerate antithrombin III neutralization of* the clotting serine proteases Thus heparin has a major role in preventing thrombosis initiated via the intrinsic clotting system as well as in the final common pathway leading to fibrin gel formation and irreversible platelet aggregation In this role heparin acts as a catalyst[58,60] requiring anti thrombin III for its efficacy and increasing the rate of the inhibitor-protease *reaction* without being consumed and without altering the final products of the reaction[41]

Coumarin compounds Two comprehensive reviews of the mechanism of action of coumarin compounds and their effect on coagulation have recently been published[61,6] Warfarin (one of the more frequently used coumarin drugs in this country) acts *as an anticoagulant* by inhibiting the carboxylation of glutamic acid to γ carboxy glutamic acid residues The presence of γ car boxyglutamic acids imparts two essential proper ties to the K dependent clotting zymogens the proteins bind Ca^{2} in the physiologic range and also bind to a negatively charged phospholipid surface in the presence of Ca^{2} In man the noncarboxylated proteins are released into the circulation Thus, warfarin alters the synthesis of four K dependent zymogens factors II, VII, IX and X Although the prothrombin time reflects changes in factors II, VII, and X and is used effectively as a guide to dosage of the oral anti coagulants, the warfarin induced changes in these *zymogens have never been correlated with the* prevention of thrombosis in man or experimental animals Recently, several additional vitamin *K dependent proteins have been isolated from* plasma[63,66] One is capable of being activated to a protease that resembles the K dependent clotting factors and can degrade factor V[67] thus inhibiting coagulation, a second appears to have an effect on the heparin-antithrombin III reaction[68] The clinical roles of these recently identified proteins are yet to be determined

Fibrinolytic agents For almost 50 years it has been known that streptococci produced an enzyme that lysed fibrin[68] and for nearly 20 years it has been known that this material streptoki nase can potentiate the dissolution of thrombi in man It was also recognized that urokinase an enzyme produced by the kidney and found in human urine has the capacity to potentiate the *dissolution of clots*

Both proteins, as activators of the fibrinolytic system act by combining with plasminogen to *form a 1 1 complex* of activator and plasminogen which by proteolytic cleavage converts plasmin ogen to plasmin[71] Dissolution of the thrombus probably results from the action of either the activator or the formed plasmin within the thrombus The enzymatic effect of plasmin on zymogens in flowing blood is usually feeble because of the presence of plasmin *inhibitors in the circulation* Immunological problems compli cate the use of streptokinase Morever, in patients with *recent streptococcal infection* a large load ing dose of the drug may be required to overcome the immunological inhibition of streptokinase action and, in some of these patients streptoki nase may be ineffective in therapeutic doses Streptokinase is more readily and more inexpen sively produced than urokinase

prior to therapy that is increased after heparin administration will demonstrate that heparin is circulating One study has claimed that if the partial thromboplastin time is not maintained above a given level in heparinized patients the likelihood of thrombosis is increased [9] Neverthe less in an individual patient there is as yet no technique for determining the minimum amount of heparin necessary to prevent further thrombo sis The issue is further complicated particularly in the first few days of therapy by the fact that it is not possible to distinguish progression of thrombosis from fracture of a leg vein thrombus and its subsequent passage to the lung—a phenomenon unaffected by anticoagulant drugs

Hemorrhage while it complicates dosage schedule at the same time simplifies the decision making process for in reality risk of hemorrhage controls dosage at least after 48 hours of heparin ization It is rare in a hemostatically competent patient to encounter spontaneous hemorrhage during the first 48 hours [96, 9] of a regimen of 30 000 to 40 000 units of heparin per day Subse quently the risk is real and unpredictable even by the partial thromboplastin time This risk can be aggravated by the administration of aspirin or other platelet antiaggregants by heparin asso ciated thrombocytopenia and by trauma from surgery invasive vascular procedures intramus cular injections and the occasional reported and unreported minor injuries that hospitalized patients may sustain Some protection from the consequences of hemorrhage can be obtained by *minimizing these traumatic events and by* frequent hematocrit determinations and platelet counts

It is for the reasons just mentioned that the dose of heparin in the majority of patients should be reduced after 48 hours to the range of 20 000 to 25 000 units/day provided the throm botic episode is not progressing as determined by clinical and laboratory finding If anticoagula tion is to be continued beyond the hospital stay warfarin therapy can be initiated In this regard it is probably desirable to overlap the oral anti coagulant with heparin for six days *after* the prothrombin time has reached the therapeutic level These recommendations are not ideal but are dictated by current limitations in our knowledge of the pathogenesis of venous throm boembolism and the pharmacology of heparin It is believed that this regimen together with the precautions recommended will protect the vast majority of patients from further venous throm boembolism and diminish significantly the amount of hemorrhage induced by heparin—pres ently a major source of in hospital drug related deaths in reasonably healthy patients [10] As research advances in both these areas the clinical guidelines will be sharpened

In patients with massive acute pulmonary embolism investigators have recommended as much as 120 000 units/day for the first 24 hours of treatment [1, 3, 104] Others have stated that 60 000 units are adequate [1, 7, 10] Since there are no guides from clinical trials these large dosage schedules should be reserved for patients with massive pulmonary embolism and shock Such high dosages should be reduced to the medium dose range 12 to 24 hours after therapy is instituted and then further reduced as clinical progress dictates The risk of bleeding on the highest regimen is reported to be low in the first 24 hours [107, 9] and there appears to be little purpose in doing clotting assays in this situation [1, 9] These observations may merely demonstrate that large amounts of heparin may not produce hemorrhage within the first few hours of administration rather than reflecting the amount of heparin actually required to prevent further thrombosis in these patients

METHODS OF ADMINISTRATION There are at present three accepted methods whereby heparin is administered subcutaneous injection intermit tent intravenous injection and continuous intra venous injection

Subcutaneous injection has been used almost exclusively for low dose heparin regimens This method results in a prolonged low plasma level of heparin [9, 12]—a situation which is required to minimize bleeding intraoperatively and postoper atively while maintaining an antithrombotic effect For medium dose regimens both intermit tent and continuous intravenous injections have been used Data regarding the relative frequency of bleeding complications with these two regi mens have been conflicting Two studies con cluded that there was a greater incidence of bleeding with intermittent intravenous than with continuous intravenous administration [1, 3, 114] Two other reports found no difference in hemor rhagic complications between continuous and intermittent intravenous therapy [1, 3, 11] In all of the studies however the units of heparin/24

Table I Heparin regimens

Dose (USP units/24 hrs)	Route	Clinical indications
Low dose 10 15 000	Subcutaneous	(1) Elective abdomino thoracic surgery (2) Acute myocardial infarction (3) Disseminated intravascular coagulation
Medium dose 20 60 000	Intravenous (continuous or intermittent)	(1) Active venous thromboembolism (2) Disseminated intravascular coagulation
High dose 60 000 100 000*	Intravenous (continuous)	(1) Massive pulmonary embolism with shock

See text for limitation of duration in days of the larger doses

whether correction of increased platelet consumption can be correlated with an antithrombotic effect is still questioned

Sulfinpyrazone Several reports have indicated a favorable effect of sulfinpyrazone on recurrences of TIA[86 88] and in one of these trials a survival benefit was noted[87] Sulfinpyrazone also appeared in this latter trial to have a survival benefit among patients with a previous myocardial infarct A large TIA trial utilizing sulfinpyrazone is still ongoing

Recently a randomized, double blind multicenter trial comparing sulfinpyrazone (200 mg four times daily) with a placebo has demonstrated a significant reduction in sudden cardiac deaths among treated patients compared to the control group during the first year after myocardial infarction[89] Although the basis for the benefit has not been established, the results are very striking

Among patients with prosthetic mitral valves sulfinpyrazone has returned shortened platelet survival times toward normal[9] although a significant antithrombotic effect has not yet been demonstrated

Dipyridamole In a single trial of dipyridamole among patients with cerebrovascular disease no benefit was recognized[91] Similarly in a large number of trials of this drug among patients with coronary artery disease no benefit has been found In patients with mitral valve disease shortened platelet survival has been returned to normal, but an antithrombotic benefit has only been demonstrated when dipyridamole was used with another antithrombotic agent[92]

Heparin

Dose Heparin has been employed most effectively to prevent venous thromboembolism in low doses prior to the onset of intravascular coagulation and in larger doses to prevent progression after a thromboembolic event has occurred Table I lists currently accepted dose regimens, routes of administration, and indications for therapy Details on the efficacy and safety of the low dose regimens on a variety of conditions have been recently published in this Journal[93] and elsewhere[94] What requires discussion here is the use of heparin at higher doses after the thrombotic event

Once deep venous thrombosis or pulmonary embolism has occurred low dose heparin regimens are inadequate For patients in whom the extensiveness of thrombosis is not great, as estimated clinically or with laboratory guides a treatment range of 20 000 to 60 000 units/day encompasses most of the reports[95] In the majority of these studies heparin was given by intermittent intravenous injection, in many by constant infusion Most of the regimens were in the narrower range of 30 000 to 45 000 units/day Some investigators have used body weight in determining the daily dose, but most have not Some reports recommend lower doses for older women, others do not Although many investigators use some clotting assay as a guide to dosage several do not Clearly it is difficult to provide definitive dose recommendations in the absence of firm clinical data Moreover the decision making process is further complicated by the fact that the antithrombotic effect and the hemorrhagic risk do not proceed in parallel and as will be seen it is the latter which is usually the more critical of the two in determining dose

Our interpretation of the literature suggests that 30 000 to 40 000 USP units/day by the intravenous route (either by continuous infusion or by bolus on a four hourly schedule) will be antithrombotic in the large majority of patients This recommendation assumes that the quantity of plasma antithrombin III is normal—a determination that can be made prior to the institution of therapy by any one of several available assays[96 97] In addition a normal partial thromboplastin time

that long term anticoagulation not be attempted If however underlying heart disease is recognized then long term anticoagulation appears justified although such a view is still controversial

Fibrinolytic agents Streptokinase or urokinase have been tried in a host of conditions including acute myocardial infarction stroke peripheral arterial occlusion retinal artery occlusion priapism DIC and thrombosed valve prosthesis with inconclusive or negative results In two clinical trials among patients with pulmonary embolism these thrombolytic agents showed improvement in angiographic and hemodynamic measurements [13, 134] Similarly lysis has been accelerated in patients with extensive deep venous thrombosis [35] and in other studies thrombolytic agents cleared at least temporarily partially occluded arteriovenous cannulae [136] Thrombolytic agents are primarily effective against recent thrombi

Current recommendations are for their use primarily in acute massive pulmonary embolism or extensive venous thrombosis How well these recommendations will withstand the test of time cannot be judged at present For it is clear that thrombolytic agents entail a substantial risk of hemorrhage should not be used concurrently with heparin or the coumarin compounds and particularly for streptokinase present the added problem of allergic reactions Following discontinuance of fibrinolytic therapy moreover heparinization is usually necessary to prevent rethrombosis The practical problems involved in the safe and effective administration of these drugs for the limited clinical situations in which they may be helpful adjuncts strongly suggest that their use for the present be limited to institutions with knowledgeable coagulation laboratory support

Dextran Both Dextran 40 and Dextran 70 have been used to prevent venous thromboembolism and effective results have been obtained in surgical patients Whether it is superior to heparin or warfarin has not been established although it may have a special role in orthopedic surgery and in patients with trauma [1, 7]

General comment

The impact of thromboembolism on mortality and morbidity is impressive It is involved substantively in deaths from cardiovascular cerebrovascular and renal disease it contributes to occlusions of arteries veins microcirculatory vessels and wherever blood comes into contact with a foreign surface In atherosclerosis thrombosis plays a role in the terminal vascular occlusion [134] in the enlargement of the plaque [13] and possibly in the origin of the atheroma itself [5]

A broad armamentarium of pharmacologic agents is now available to prevent or treat thromboembolic episodes It is possible somewhat arbitrarily to divide these compounds into three groups (1) drugs that inhibit the coagulation cascade so that insufficient thrombin is formed to initiate or propagate a thrombus (heparin and warfarin) (2) compounds that inhibit or remove clotting constituents essential to the formation of thrombi (platelet antiaggregants dextran and ancrod) and (3) agents that destroy already formed thrombi (streptokinase and urokinase) The choice dose duration and regulation of drug therapy—or in some instances the choice of drug combinations or drug sequences—may depend on the result desired the morphology of the thrombus the vascular bed involved the sex age and hemostatic competency of the patient the presence of other concurrent disease states and finally the risk–benefit ratio of each agent in any particular clinical setting Fortunately this decison making process is often easy but at other times particularly where knowledge is still incomplete definitive solutions may remain elusive None of these agents however effective will remove the factors causing thrombosis nor will they invariably prevent previously formed thrombi on endocardium arteries and veins from embolizing to distal portions of the circulation

It is clear that several of these problems can only be resolved by further insights into the molecular events that either initiate intravascular coagulation or account for the antithrombotic actions of chemically diverse compounds Despite the complexity expense duration and at times the frustration of clinical trials they remain in many instances an important court of last appeal complicated though they may be by unanticipated errors in design low event rates ethical and legal considerations and retrospectively premature decisions to test a particular compound in a given condition That trials are initiated when knowledge of the pharmacologic effects of the agent to be tested are incomplete and the apparent vagaries of the natural history of the underlying disease process not entirely

hours were less *in the continuous compared to the* intermittent groups One may conclude, from the available data that either technique may produce hemorrhagic complications if full dosage schedules are maintained beyond 48 hours

Since it has been demonstrated that the rate of heparin clearance is increased following pulmonary embolism,[116, 117] it is suggested that, when using intermittent intravenous therapy for this condition, heparin be administered every four hours If, however, a regimen of intermittent therapy every six hours is used, some assay should be performed on a plasma sample obtained 5½ hours post heparin administration to insure the maintenance of an antithrombotic effect for the entire period between injections

One observation that may complicate the *management of heparin therapy is the possibility* of a heparin induced decrease in the quantity of antithrombin III It has recently been reported that some patients receiving either continuous or intermittent intravenous heparinization exhibited a plasma inhibitor decrease to levels as low as 67 per cent of initial levels[118] During therapy, *however, these patients are adequately anticoagulated* even if antithrombin III is depressed by heparin If, however this observation is a general phenomenon it will cause difficulty in the interpretation of assays used to monitor therapy Since the anticoagulant action of heparin is dependent on the quantity of antithrombin III in *plasma,*[119] *assays such as the partial thromboplastin* time and the whole blood clotting time may fail to reflect the anticoagulant effect of the drug Attempts to attain therapeutic levels of heparin as judged by these assays, may result in excess heparinization with the concomitant risk of hemorrhage, when heparin is actually functioning optimally *without a dose increase*

When heparin is discontinued the drug induced depression of antithrombin III returns to normal in 24 to 48 hours During this time period the patient may be at potential risk of thrombosis[11] providing another reason for overlapping warfarin with heparin

Oral anticoagulants Coumarin compounds have had some success in diminishing the recurrence of TIA, but have had no clear cut effect in reducing the subsequent incidence of stroke or death[120]

By far the largest number of trials have involved the use of the oral anticoagulants in the treatment of acute myocardial infarction The data from these trials have been evaluated in a variety of ways[121-123] If one assumes that on average, 20 per cent of patients *hospitalized for* acute myocardial infarction will die and that of these deaths 1 per cent result from pulmonic and 1 per cent from systemic emboli and that oral anticoagulants can prevent 80 per cent of these thromboembolic catastrophies, then a small but meaningful benefit could be achieved among the 500,000 *patients annually hospitalized for acute* myocardial infarction in this country[124] What effect the trend to early hospital discharge of patients with uncomplicated acute myocardial infarction[125] may have on patient selection, or the duration or value of oral anticoagulants in this disorder remains to be determined

Data *are available to suggest that oral anticoagulants* will diminish systemic emboli in patients with significant mitral stenosis[126] as well as with prosthetic valves[127] In the latter situation this prophylactic gain is claimed to be augmented by supplementation with dipyridamole[92] or aspirin[128] At the same time, improvements in valve *prostheses are believed to have resulted* in a decrease in their intrinsic thrombogenicity

Oral anticoagulants of course, share with heparin a place in the prevention of venous thromboembolism

The contraindication to oral anticoagulants dosage laboratory control and the management *of major hemorrhage,* have been covered in prior reviews[129] It is reasonable to initiate warfarin therapy without a loading dose[130] and it is critical to appreciate that there are an ever increasing number of drugs that may potentiate or antagonize the anticoagulant action of the coumarin compounds[131] When patients on anticoagulants have other drugs deleted from or added to their therapeutic regimen frequent prothrombin time determinations will permit appropriate coumarin dose regulation Finally, it must be recognized that there are occasional *patients who* are congenitally resistant to coumarin therapy[132]

The cardiologist is frequently confronted with the decision as to whether to anticoagulate the patient with episodic or fixed atrial fibrillation or with the other arrhythmias associated with systemic embolism If thorough investigation reveals no underlying heart disease in a patient (particularly a young individual) with atrial fibrillation the risk/benefit ratio would suggest

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unravelled, only adds further difficulty to the decision making process However, one cannot always wait until all questions have been answered, and under similar conditions, therapeutic triumphs have occurred in other fields In any event, progress with antithrombotic therapy continues to be made, even though firm data are only available in certain areas, and the physician is still confronted with difficult decisions where clear therapeutic formulations have yet to be achieved

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Table 1 Uses of diuretics (see text for details)

Indication	Agent: Thiazides Chlorthalidone Metolazone	Furosemide Ethacrynic Acid	Spironolactone Triamterene
Edema forming states (CHF cirrhosis nephrosis)	+	++	+
Hypertension	++	+	+
Hypercalcemia	−	++	−
Hypercalciuria	++	−	−
Diabetes Insipidus	+	−	−
Syndrome of inappropriate secretion of ADH	−	+	−
Renal tubular acidosis	+	+	−
Renal failure	−	+	−

tration of these drugs reduces urinary calcium excretion and makes them useful in the treatment of patients with idiopathic hypercalciuria and renal calculi [1] Agents in this group impair urinary diluting capacity (by their effect on the ascending limb or diluting segment of the nephron) and thus have been useful in the treatment of diabetes insipidus especially of the nephrogenic type [2] Finally since these drugs increase urinary hydrogen ion excretion [13] they may be employed in the treatment of renal tubular acidosis

Side effects of this group of diuretics are numerous but usually mild Hypokalemia is common and may be attributed to multiple factors including increased urine flow rate and increased delivery of sodium or poorly resorbable anions (bicarbonate or phosphate) to more distal sites where potassium is secreted Hypokalemia is often clinically insignificant except in the edema forming states where exaggerated secondary aldosteronism may contribute to the potassium deficit [4] Treatment though less than ideal may be indicated when deficits are severe The therapeutic alternatives include reduction of diuretic dose (counterproductive) increase in dietary potassium (ineffective) administration of supplemental oral potassium (unpalatable) or addition of one of the potassium sparing diuretics (reliable but expensive) Accompanying the hypokalemia there is often a mild hypochloremic alkalosis caused both by indirect and direct factors [2] which unlike the situation with the organomercurials does not impair the action of the diuretics

Hyperuricemia is also common and results from a decrease in urinary excretion of uric acid [5]

Occasionally clinical gout is evoked by the diuretics and requires treatment with standard agents In this regard it is pertinent to warn of the potential hazard of treating diuretic induced hyperuricemia with allopurinol This combination of drugs has been reported to cause serious life threatening reactions and should be avoided Mild thrombocytopenia has been described[17] which is usually reversible on discontinuing the drugs Less common side effects of these agents include hyponatremia resulting from a combination of salt losses excessive antidiuretic hormone release potassium depletion and impairment in diluting capacity[18] hyperglycemia usually mild[1] azotemia from excess diuresis and consequent volume depletion or from acute interstitial nephritis [9] and various allergic reactions common to all sulfonamides (skin rash photosensitivity narrow depression) Rarely reported complications of therapy include paradoxical edema [21] hemolytic anemia [2] or allergic pneumonitis [23] Despite this imposingly long list the distal tubular diuretics have been employed usefully and safely over the past 30 years

Ethacrynic acid and furosemide

These agents are loop of Henle diuretics Ethacrynic acid is an aryloxyacetic acid derivative developed in the search for a potent inhibitor of sulfhydryl containing enzyme systems [24] After ingestion and rapid absorption the drug is chemically modified to its active form ethacrynic-cysteine [25] Furosemide is a sulfonamide analogue akin to the thiazides yet its renal actions are similar to ethacrynic acid [6] It too is rapidly absorbed but acts without modification on the

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C DeGraff and Julian Frieden

Diuretics

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The development of clinically useful diuretic agents has been an important advance of the past 30 years Until then, the organomercurials were the most commonly employed diuretics but their usefulness was limited by the need for parenteral administration [1] However, the finding in the 1940's that benzoyl and heterocyclic sulfonamides were inhibitors of carbonic anhydrase[2] and could increase urinary sodium excretion[3] stimulated a search for other compounds which might act as potent oral diuretics The purpose of this report is to describe the mechanisms of action, clinical uses, and side effects of some of these orally administered agents

A diuretic, by definition, is a compound which increases the flow of urine by any means Thus a diuresis may be obtained by aminophylline or glucocorticoids, which increase glomerular filtrate rate, by maneuvers such as plasma volume expansion or by a wide variety of agents which increase cardiac output However, this discussion will be limited to compounds which act directly on the kidney, specifically on the renal tubule to increase the excretion of salt and water

Thiazides chlorthalidone and metolazone

The agents in this group are distal tubule potassium wasting diuretics Though differing chemically from each other they have similar effects on the nephron Chlorothiazide developed first, and hydrochlorothiazide the most widely used benzothiadiazine compounds were discovered as carbonic anhydrase inhibiting analogues of sulfanilamide [4] Chlorthalidone is a non sulfonamide phthalimidine and metolazone is a quinazoline derivative of sulfonamide After oral administration, the drugs are absorbed rapidly and then filtered and secreted (via the organic acid secretory pathway) into the renal tubular lumen [5] There they exert their primary effect by inhibiting active sodium transport in the cortical portion of the ascending limb and in the distal convoluted tubule where approximately 10 per cent of the filtered sodium is normally reabsorbed In addition, these compounds have varying degrees of carbonic anhydrase inhibitory activity, but this action does not account for a significant portion of their diuretic effect Differences in potency of these agents relate principally to their duration of action Thus the benzothiadiazines exert their effect for 6 to 12 hours while metolazone due to strong protein binding and considerable enterohepatic recycling [6] exerts a diuretic effect for 24 to 48 hours The dose response curve for these drugs is flat above the recommended maximal dose (1500 mg /day chlorothiazide 150 to 200 mg /day hydrochlorothiazide, 200 mg /day chlorthalidone, 10 to 20 mg / day metolazone), and the use of additional drug increases side effects without a significant increase in the diuretic action [7]

The distal tubule diuretics are useful in a wide variety of conditions (Table I) They are employed in the edema forming states (congestive heart failure, cirrhosis and nephrotic syndrome) to directly increase urinary sodium excretion However if volume depletion is present or develops during treatment distal salt delivery may be reduced Under these circumstances the agents may become less effective in promoting a diuresis Distal diuretics are also useful in the treatment of hypertension because of their relatively long duration of action They exert both renal (diuretic) and non renal (vasodilatory) effects each of which contributes to the lowering of blood pressure [8] The chronic adminis

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Received for publication June 30 1978

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0002 8703/78/120824 + 04$00 40/0 © 1978 The C V Mosby Co

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renal tubule Both agents exert their primary effect by inhibiting active chloride transport in the thick ascending portion of Henle's loop and are thus capable of inhibiting more than 20 per cent of the filtered salt load Moreover, unlike the distal tubule drugs, the loop diuretics have an almost infinite dose response pattern and in large doses (300 to 600 mg ethacrynic acid 1000 to 1500 mg furosemide) are effective even in the presence of renal insufficiency [7] Thus they are extremely potent diuretics with a rapid onset (30 to 60 minutes) of effect, limited only by a relatively short (4 to 6 hours) duration of action

The loop diuretics are most useful in the severe edema forming states (Table I) where their potency almost always insures a substantial diuresis However, they may continue to promote salt and water losses in the face of severe volume depletion, a characteristic that also makes them potentially more dangerous Because of their shorter duration of action, they are probably no more effective than thiazides in the treatment of hypertension [27] although this fact has been ignored by most clinicians Unlike the distal diuretics which reduce urinary calcium, the loop diuretics promote renal calcium excretion and are employed in the treatment of hypercalcemia [28] Like the thiazides they promote urinary hydrogen excretion and are used in the management of renal tubular acidosis Finally, since these agents act on the ascending limb of Henle's loop (the concentrating segment) to impair urinary concentration they have been used, with infusions of hypertonic saline, for the rapid correction of hyponatremia in the syndrome of inappropriate secretion of antidiuretic hormone [9]

Side effects of the loop diuretics are similar to those of the thiazides with a few important differences They do not cause hypercalcemia Ethacrynic acid which is not a sulfonamide is less frequently associated with hypersensitivity reactions and hyperglycemia than furosemide but does produce more gastrointestinal side effects Both drugs cause transient nerve deafness, especially when employed in high doses in azotemic patients occasionally the deafness is long lasting after ethacrynic acid [30] Less commonly reported adverse reactions for furosemide include agranulocytosis,[31] interaction with chloral hydrate [3] and hepatic necrosis [33] Despite these side effects the loop agents have been widely used to effect a rapid and reliable diuresis

Spironolactone and triamterene

These agents in this group are distal tubular potassium sparing diuretics Spironolactone is a specific competitive inhibitor of the cellular binding of aldosterone [34] Its action is thus directly related to the circulating level of endogenous mineralocorticoid In contrast, triamterene a pterydine derivative is not dependent on circulating levels of aldosterone and has a different mechanism of action from spironolactone Nonetheless these agents have identical effects on urinary composition [5] The drugs are absorbed and act in their native state in the distal nephron, to inhibit sodium reabsorption and to block potassium and hydrogen ion excretion They are weak natriuretic drugs when used alone, capable of inhibiting only the 2 to 3 per cent of the filtered salt load which is delivered to the distal nephron (even less during volume depletion)

Since the distal tubule potassium sparing agents are not potent natriuretic drugs they are employed in the edema forming states and in hypertension (Table I), principally in combination with the other diuretics for a small additive diuresis and to prevent hypokalemia However, spironolactone alone in higher doses (400 to 600 mg /day) may be useful in the management of primary aldosteronism

The major side effects of the potassium sparing agents related to their tubular actions are hyperkalemia and less commonly, metabolic acidosis [35, 36] These complications are particularly frequent either in patients receiving potassium supplementation or with renal insufficiency thus these agents are contraindicated under these circumstances Gynecomastia and hirsutism are troublesome side effects of spironolactone [37] and both drugs in this class cause mild gastrointestinal upset in occasional patients Nonetheless the distal potassium sparing agents when used properly, have added a significantly useful component to modern diuretic therapy

In summary the last 30 years has seen the development of many useful oral diuretic agents active at different sites in the renal tubule Rational use of these agents in the edema forming states in hypertension or in other special situations requires knowledge of their pharmacology mechanism of action and side effects With understanding and careful use diuretics have become some of the most valuable widely used drugs in the modern therapeutic armamentarium

more advantageous than right sided A V sequential pacing If a quadripolar electrode were to be used in the coronary sinus site differences in the positions of the electrode pairs may further accentuate the stimulus threshold differences for the two chambers, with the proximal and distant pairs being used for atrial and ventricular stimulation respectively Thus the technique here described with possible further refinements and an appropriately designed pacing device may obviate the necessity of two electrode insertions for the purposes of sequential A V pacing

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A reevaluation of intravenous quinidine*

Quinidine is an effective and widely used antiarrhythmic agent usually given orally for long term arrhythmia control Although lidocaine and procainamide are generally recognized as agents of choice for emergency control of most ventricular tachyarrhythmias, some arrhythmias are refractory to these agents. Furthermore many supraventricular arrhythmias respond poorly to lidocaine and procainamide Thus clinical situations often arise in which the need for rapid achievement of therapeuti quinidine levels necessitates parenteral therapy The intramuscular (IM) route has been the preferred mode of parenteral quinidine therapy largely due to sporadic reports of unfavorable reactions to quinidine by the intravenous route Recent studies on the pharmacokinetics of IM drug administration as well as recent experience with intravenous quinidine suggest that the question of the optimum parenteral route for quinidine should be reconsidered

Intramuscular administration of many agents results in slow unpredictable and sometimes incomplete drug absorption. Poorly water soluble drugs are often prepared for injection in irritating oily solvent vehicles After injection the drugs may precipitate at the injection site resulting in considerable local pain and tissue damage as well as poor drug absorption Although total quinidine bioavailability by the IM route is comparable to that observed after oral administration of q unidine sulfate absorption is erratic and occasionally non linear Furthermore quinidine injections are associated with moderate to severe pain and substantial increases in serum creatine phosphokinase

It is widely perpetuated dogma that intravenous quinidine is too hazardous to be acceptable Specific hazards are thought to include profound hypotension " exacerbation of malignant arrhythmias and cardiac arrest Some clinicians have stated that intravenous quinidine is never or hardly ever indi ated because of these risks

Two large series and a number of case reports appear to constitute the evidence upon which these recommendations rest (Table I) Critical assessment of these cases indicates that most of the patients with adverse reactions to intravenous quinidine were virtually moribund before the drug was given Their arrhythmias were complicated by severe congestive heart failure hypotension or shock Moreover the patients often were receiving digitalis and some appeared to have overt digitalis toxicity In five cases quinidine was infused too rapidly and electrocardiographic (ECG) signs of toxicity were not heeded The mode of death was not always documented, and even the authors acknowledged that death may have occurred despite rather than because of quinidine

*This work was do i part duri g the tenure f research gr nt in aid ward from th Ameri an He rt Associatio Wes ern Massa husetts Di isi d th Am rican He rt Association Massa husetts Affiliate Inc No 1-506- 6 (to Dr Greenblatt) Dr Woo is the recipient of a rese ch fell wship (HL-05?23) from the United States Public H alth Service

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Annotations

Sequential atrioventricular pacing with a single bipolar electrode catheter

Electrophysiologic and hemodynamic considerations have perhaps never found a better technologic interface than the highly specialized sequential atrioventricular mode of cardiac pacing Although the exact extent of its applicability is yet to be established its usefulness in the management of certain select clinical problems has been well documented [1-3] One of the drawbacks of the technique has been the necessity of separate atrial and ventricular electrodes A specially designed six polar catheter has been one proposed solution to this problem [4, 5] but experience with it is still limited Despite the recent development of specialized atrial pacing electrodes the *coronary sinus remains one of the best and most reliable* permanent atrial pacing sites [6] Since the left ventricle can also be paced from an electrode in the coronary sinus we tested the possibility of sequential A V pacing via a single bipolar electrode catheter placed in the coronary sinus The feasibility of this undertaking depended on a sufficient difference between the left atrial and left ventricular pacing thresholds from the coronary sinus site to allow selective stimulation of the two chambers with a reasonable margin of safety *Fig 1 demonstrates this technique in a patient in* whom a bipolar electrode catheter had been temporarily inserted into the coronary sinus during a diagnostic procedure being carried out for a different purpose The atrial pacing threshold was found to be about one fourth of the ventricular threshold The bipolar electrode was connected to two isolated stimulators set at 1 5 times the pacing threshold of each chamber and triggered sequentially by a digital timing device such that the lower voltage stimulus was followed by the higher one after a variable delay which effectively determined *the resulting A V delay So long as this delay was less than the* atrial refractory period the atrium would not be restimulated with the ventricular impulse The application of this technique resulted in successful A V sequential pacing at variable rates and atrioventricular delays

Previous evidence showing that left ventricular pacing resulted in better cardiac output than right ventricular pacing[4, 8] may possibly render this mode *hemodynamically*

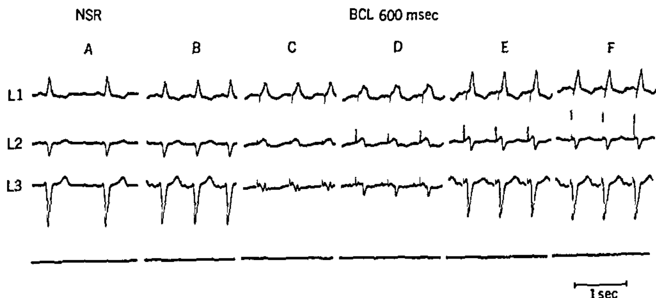


Fig 1 Simultaneous tracings of electrocardiographic Leads 1 2 and 3 and stimulus timing signals *(bottom)* The QRS configuration during normal sinus rhythm *(panel A)* and during atrial pacing via the coronary sinus electrode *(panel B)* are identical *In panel C* the left ventricle is paced through the same electrode utilizing a higher current *In panels D E and F* low and *high intensity stimuli are applied* in pairs with delays of 100 150 and 200 msec respectively With delays of 100 and 150 msec *(panels D and E)* the QRS configuration is intermediate between the sinus and ventricular paced configurations and is the result of different degrees of fusion between ventricular *and supraventricular* activations When the spontaneous P R interval is exceeded (delay 200 msec *panel F*) the QRS configuration is again identical to that during sinus rhythm or atrial pacing In this instance the *ventricular* stimulus is too late to affect the ventricular depolarization pattern resulting from conduction of the atrial impulse

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effects were encountered ECG changes characteristic of quinidine effects occurred in all patients these rapidly reversed following termination of the infusion as did other symptoms and signs. Results from other laboratories are similar Conrad and colleagues infused quinidine at a rate of 0.5 to 1 0 mg /Kg /minute to nine ho pitalized patients with out significant adverse effects Ueda and associates and Hirschfeld and co-workers described intravenous infusion of quinidine gluconate at .3 to 4 mg /Kg /minute to 27 cardiac patients, 12 of whom had underlying conduction defects They noted no increase in the degree of block or in ventricular ectopic activity Mild asymptomatic decreases in blood pres sure occurred in 15 patients this responded to elevation of the legs and slowing or termination of the infusion Two patients had more severe hypotension with nausea and diaphoresis. The syndromes resolved without sequelae with termination of the infusion Therapeutic serum levels (3 to 7 μg/ml) were achieved within 22 minutes in 15 of the 16 patients who received 2 6 to 5 4 mg /Kg of quinidine base Pot ntially toxic serum quinidine concentrations did not occur in any patient

Many other reports are available documenting the safe use of intravenous quinidine in the context of more general evaluations of antiarrhythmic therapy

Quinidine administration by *any* route is not without risk and the risk is especially great in certain susceptible individu als. For patients needing parenteral therapy intravenous infusions are clearly preferred to IM injections. The IM route is painful and characterized by erratic and unreliable absorp tion Furthermore it is impossible to halt further drug absorption if untoward ECG or hemodynamic reactions devel op following IM injection Rapid intravenous infusion of quinidine with resulting plasma concentrations in the known toxic range would certainly be expected to carry unacceptable hazard Because quinidine is rapidly and extensively distri buted to tissues, potentially toxic serum concentrations are not likely to be reached during a slow controlled infusion of a therapeutic dose at 0 3 to 0 4 mg /Kg /minute If untoward ECG or hemodynami effects do develop in susceptible indi viduals during the infusion they can be reversed readily by stopping the infusion Thus well controlled slow intravenous infusion, with due regard for plasma levels achieved appears to represent a safe and reliable mode of quinidine administra tion for patients needing parenteral therapy

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Table I Reports of adverse reactions to intravenous quinidine

Reference	Number of fatalities/total cases	Characteristics of patients with adverse reactions: Age	Disease state(s)*	Clinical status prior to quinidine administration	Quinidine dose and rate of injection	Adverse reactions
8	0/9	?	IHD, PVT	Hypotension	Infusion of 15 mg/min to maximum total of 2300 mg	Transiently exacerbated hypotension in one patient after 650 mg
9	1/1	57	Acute MI, PVT	Semi moribund, Cyanotic, Dyspneic	450 mg as a bolus following 1 8 gm given in prior 24 hours	Agitation then collapse
10	4/34	5?	RHD, Severe CHF, PVT	Moribund	600 mg over 20 min	No details given
		63	Uremic coma, RHD	Comatose	300 mg given over a few minutes	Respirations ceased
		58	Acute MI	Extreme shock	1200 mg over 30 min	No details given
		51	RHD, AF	Shock	100 mg time not specified	No details given
11	4/44	66	Hypertension, CHF, Digitalis toxicity, PVT	Not stated	650 mg over 30 min	Progressive AV block then asystole
		50	Hypertension, PVT, Possible digitalis toxicity	Not stated	130 mg over 10 min	Progressive AV block then asystole
		50	Hypertension, CHF, PVT, Digitalis toxicity	Not stated	400 mg over 27 min	Progressive AV block then ventricular fibrillation
		60	Hypertension, Severe CHF, AF, Possible digitalis toxicity	Coma	650 mg as a bolus	Progressive AV block then asystole
12	0/2	52	IHD, PVT	Stable	900 mg over 300 min	Seizure then recovery
		47	PVT	Stable	650 mg as a bolus	No ill effects
13	0/1	?	PVT	Stable	450 mg as a bolus	Transient unconsciousness then recovery
14	0/1	41	PVT	Stable	2650 mg time not specified	Seizure transient unconsciousness then recovery

CHF = congestive heart failure IHD = ischemic heart disease MI = myocardial infarction PVT = paroxysmal ventricular tachycardia RHD = rheumatic heart disease AF = atrial fibrillation

Finally it is clear that quinidine administration by *any* route can produce hypotension [3] a paradoxical increase in ectopic activity [4] or even life threatening ventricular tachyarrhythmias in particular susceptible individuals [7] It may well be that some of the intravenous quinidine fatalities reported in the older clinical literature were due to the patient s sensitivity to quinidine *per se* rather than to the route of administration

Recent evidence suggests that contrary to popular dogma well controlled and monitored intravenous infusions of quinidine at appropriately slow rates constitute a safe and reliable mode of quinidine administration We have infused quinidine lactate at a rate of 33 mg/Kg/minute to a large series of healthy subjects aged 23 to 70 years.[8, 9, 15] Most subjects experienced perioral paresthesias and some individuals reported nausea but no important adverse hemodynamic

a need to define responsibility and accountability And this is the responsibility of the medical profession and good government even though the government is run by laymen and not by physicians If the doctors won t assume this responsibility the U S Government will—and should—and must

The answer to these problems is better education and practices in the medical schools and hospitals and the consideration of ethics morals and considerate practice in the medical curriculum

There is a need for better training in bedside medicine and cardiology with greater compassionate consideration of the sick man s dollar Excellent bedside cardiology is much more difficult but more rewarding to the physician than excelling in a single procedure or the operation of one gadget The master cardiologist does not routinely need these expensive and hazardous examinations and tests However he knows when he needs them and uses them selectively Good well trained and master clinicians can obtain the necessary clinical information at the bedside much more thoughtfully less expensively and without risk to the patient But who is to train elegant or master bedside cardiologists? Bedside clinicians are disappearing and new ones are not appearing to replace them Surely those who must depend upon catheters treadmills Holter monitors vectorcardiograms echocardiograms coronary care units etc for management of the cardiac patient cannot train bedside cardiologists The need in cardiology is not for more gadgets more tests and more costs but rather for more and better clinical education What the master cardiologist can do for his patient at the bedside with little cost to the U S Government insurance companies and patients and their families is astounding There is a need to value merit and good practice and not measure success by money material things or political and administrative advancement These are problems that can best be resolved by the medical profession itself

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Favorable effects of prolonged nitroglycerin infusion in patients with acute myocardial infarction

The prognosis of acute myocardial infarction has been closely related to the extent of cardiac damage Necrosis is a dynamic process and in the early period of acute myocardial infarction cells which are still in reversible injury can either progress to necrosis or retain viability Experimentally it has been shown that after coronary occlusion pharmacological interventions may decrease the development of myocardial necrosis quantified histologically and enzymatically These interventions which protect the ischemic myocardium in laboratory animals also hasten the decline of elevated precordial ST segment in animals and in patients Nitroglycerin accelerates the fall of ST segment elevations in patients with acute myocardial infarction suggesting that the extent of myocardial damage may be decreased In those patients the favorable effects of nitroglycerin on ischemia were demonstrated with an infusion maintained for only a few hours a longer infusion might be considered as a real treatment and could reduce complications and mortality of acute myocardial infarction

Seventy four patients with acute myocardial infarction (admitted within 24 hours of the onset of chest pain) were randomized to control (35 patients) or to nitroglycerin treatment (39 patients) groups Patients with initial cardiogenic shock and patients not in clinical shock but with systolic arterial pressure less than 90 mm Hg were excluded from this study Nitroglycerin was initially infused at a rate of 15 μg/minute and the dose was slowly increased every 10 minutes until a fall in systolic arterial pressure of 70 mm Hg was obtained The first 12 patients were treated during 24 hours since there were only few side effects nitroglycerin infusion was maintained for 5 to 7 days in the 27 other patients Infusion began 10 1 ± 0 9 hours after the onset of chest pain and the average rate of nitroglycerin infusion was 50 8 ± 3 ? μg minute All patients with anterior acute myocardial infarction (nitroglycerin and 22 control patients) were studied by 30 lead precordial mapping the maps recorded on admission and 7 days later were comparatively analyzed according to Maroko s scoring system The admission maps were similar in the two groups of patients Vulnerable sites were defined as sites with ST segment elevation >1 mm and persistent R wave on initial map

Q waves appeared in 56 2 ± 14 0 per cent of the vulnerable sites in control patients versus 30 0 ± 7.3 per cent in nitroglycerin patients The sum of R wave voltages (Σ R) in these sites fell more in the control group than in the nitroglycerin group (64 0 ± 12 7 per cent versus 32 4 ± 8 1 per cent p < 0 05) The incidence of premature ventricular complexes was nearly similar in the two groups but ventricular fibrillation (VF) and ventricular tachycardia (VT) were less frequent in the nitroglycerin group (VF 0 VT four) than in the control group (VF three VT eight) The hospital mortality rate was reduced in the nitroglycerin group only two of 39 nitroglycerin patients died (two of 24 anterior infarctions 0 of 15 inferior infarctions) versus eight of 35 control patients (six of 22 anterior infarctions two of 13 inferior infarctions p < 0 0)

This preliminary study concerns a limited number of patients and does not provide quantitative information

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Of testing, treating, and charging

It is interesting that only in recent years has cardiology become so expensive and so many expensive tests have become routine In the past special procedures were used only when absolutely indicated and they were not used routinely The two step test a mild stress test was used only when definitely necessary because of its hazard and the additional cost The two step test is now replaced by the treadmill test which is *much more stressful* much more dangerous a great deal more expensive and used almost routinely by some cardiologists *but its value is yet to be established It certainly is yet to be* shown to be so routinely indicated It has not been shown to be *more informative clinically or quantitatively than Master s* two step test nor more informative than a good history physical examination and *minimal simple and inexpensive* laboratory studies Nevertheless patients are now strongly advised and led to believe that no cardiac evaluation is complete or thorough without a treadmill stress test vector cardiogram echocardiogram Holter monitor recording radioisotopic cardiac scan blood gas analyses respiratory function study apex cardiogram phonocardiogram His bundle electrogram and even cardiac and coronary angiography These tests result in charges of several hundred dollars to the patient And even if the U S Government state or municipal governments and insurance carriers pay for these tests the total cost is still borne by people often by sick people too ill to work to earn the money to pay for even part of medical services Who is to control or stop this? And is there no limit? Can one provide such services and charge them to *others without prior consideration or consent of even third* party payers? Surely no physician would allow the U S *Government insurance company or patient to visit any retail* store (medical or other) and charge purchases to him without *prior consent* regardless of how these purchases improved the health happiness or psychic state of the purchaser Why then can physicians and others order tests and consultations at random even when these procedures are not fully justified on the basis of established medical value absolute medical needs or standards of practice and merely bill the payer for them? Would any person or patient open his charge account at any department store to his doctor or any clinic or medical institution? Then why open an unlimited charge account for all and any medical tests procedures and consultations? This is what prevails to an excessive extent in American medicine today— modern medicine This *practice is especially* common among large clinical group practices and hospital groups

The policy of testing consulting treating etc without regard *to cost or prior permission* of the payer on an elective basis is most unusual in the present civilization and society or of any time in the history of man This policy would be comparable to one allowing the U S Government and insurance companies to pay for retail goods in all department stores to provide happiness and good health for all people in response to the judgment of social workers or others Purchase of anything that would make people happy would certainly better their health It would only be necessary to bill the U S Government (the American people) and insurance companies (the policy holders) and the bills would be paid without question except that the price for each item would be limited *to the level indicated in a price code established by* H E W or any other third party agency Why are the costs for *medicine given different consideration than those for* food clothing housing transportation entertainment vacations etc ? All these items can improve the health well being and happiness of people

With pressure to sell medical material and equipment by manufacturers and with the scare instilled through the press about sudden death the great killer and periodic health examinations and cardiac check ups patients are often frightened so much that they even enter bankruptcy in order not to die This is not necessary and should not be permitted in America The patient and his family with their inadequate knowledge cannot decide alone about the need for tests and treatment especially when they listen to the arguments presented and are faced with the American *tradition of* considering that good things cost a lot But who is to *control this uncontrolled practice which is spreading like a* medical economic plague? Remember much of this originates and is initiated by the U S Government research supported programs and by other government agencies and their policies and regulations as well as by insurance companies Surely special facilities must be available for occasional special and rare and well selected needs But who is to control the introduction of expensive devices by manufacturers whose primary responsibility and business is to make money? The indications uses claims of value charges and quality of service and marketing policies of apparatus procedures and tests need definition and *careful consideration by the medical profession The physicians should control* the use *of these procedures and tests and if they don t* then the U.S Government should and eventually will Not only is there a *great need to control tests* procedures equipment and apparatus but there s even greater need to decide what is a fair charge to be made to patients without their prior consent There is a need to justify at least all hazardous and expensive studies at all times More controls' But whose fault? There is

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Letters to the Editor

Main determinant of ECG voltage measurements

To the Editor

The paper by Toshima and colleagues on Correlations between electrocardiographic vectorcardiographic and echo cardiographic findings in patients with left ventricular over load which appeared in the November 1977 issue of the AMERICAN HEART JOURNAL (94 547 1977) is very interesting

It demonstrates a close correlation between voltage measurements and wall thickness in patients with pressure overload but not in patients with volume overload On the other hand a close correlation was found between voltage measurements and cavity size in volume overload but not in pressure overload I am surprised that the authors do not give the explanation which is to be found in the papers to which they refer for these findings The main determinant of electrocardiographic voltage measurements is not ventricular wall thickness but muscle mass which can be estimated from echocardiographic measurements of wall thickness and cavity size In compensated pressure overload cavity enlargement does not occur and wall thickness is the main dimension contributing to ventricular mass In volume overload both wall thickness and cavity size increase wall thickness may only be modestly increased but it is cavity size which is the main dimension contributing to ventricular muscle mass. Voltage measurements were greater in patients with volume overload than in those with pressure overload and had the authors calculated muscle mass they would have found that this was also greater in volume overload

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Reply

To the Editor

I would like to thank Dr Bennett for his letter regarding our article in AM HEART J (94 547 1977) We agree that the main determinant of electrocardiographic and vectorcardiographic voltage measurement is ventricular mass However we chose not to emphasize this since our main interest was to investigate the differences in vectorcardiographic features between patients with left ventricular (LV) hypertrophy and dilatation Our study demonstrated that QRS voltage was related to LV wall thickness in patients without LV cavity dilatation and to LV cavity size in patients without LV wall thickening These findings could be considered to have a similar meaning—that LV mass is the main determinant of QRS voltage—which was not fully mentioned in our reports It is quite likely however that other factors such as myocardial fibrosis, Brody effect proximity effect and so on play some role in the augmented QRS voltage Thus correlations between LV mass and maximum magnitude of the spatial QRS vector (r = 0.58) or SV + RV or RV (r = 0 60) were not high in our study

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Lactate production after left ventricular angiography in coronary artery disease

To the Editor

The effects of contrast medium on hemodynamic and myocardial function are well known however little is known of its effects on myocardial metabolism In an attempt to study this problem we have determined the percentage of lactic acid extraction [arterial (LA)—coronary sinus lactic acid concentration (LV) × 100/arterial concentration (LA)] during left ventricular angiography in 32 subjects. The samples were obtained at basal state immediately after the intraventricular injection of contrast medium (0 8 c c /Kg of meglumine diatrizoate) at maximum increase of left ventricular end-diastolic pressure (LVEDP continuously monitored) and 20 minutes after the injection

The patients who were all male and aged between 19 to 66

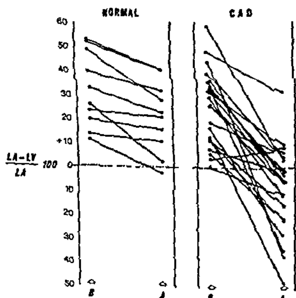


Fig 1 Maximum change of myocardial extraction ratio of lactate after left ventricular angiography (A) in normal subjects and in CAD patients (B = basal values)

however these results suggest that prolonged nitroglycerin infusion reduces significantly electrocardiographic extension and hospital mortality rate of acute myocardial infarction

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Fig 2 High power view of endocardial lesion showing acute inflammatory cells cellular debris necrotic material fibrin and erythrocytes portion of normal myocardium *(lower right)* (Hematoxylin and eosin stain)

tended to rupture easily exuding creamy purulent contents. Microscopically the outer surfaces of these masses were covered by attenuated endothelial cells the bulk of each cystic lesion consisted of acute inflammatory cells cellular debris, necrotic material platelets fibrin and exudate (Fig 2) There was no microscopic evidenc of bacteria viral inclusions fungi or neoplastic cells At the point of atta hment of these cysti lesions to the ventricular wall the mural endocardium showed no evidence of thickening inflammation or edema.

The types of les ons which most commonly affect the endocardium are bland or infected vegetations mural thrombi with or without secondary infection and abscesses which may be primary or secondary to myocardial infection The lesions described in our patient do not belong to any of these three categories. The usual endocardial vegetation is irregular rigid and friable but in the present case the mural endocardial lesions were globular soft cystic and otherwise intact until ruptured at autopsy All of these lesions appeared to be at the same stage of maturity and probably were present for no more than five to seven days A few scattered polymorphonuclear leukocytes among the myofibers of the ventricular wall probably resulted from seepage from the cystic lesions Occasional scattered necrotic muscle fibers were noted but not in direct relation hip to the cysts No myocardial abscesses were found. Of particular interest was the entirely normal condition of the cardiac valves

The proximate initiating mechanism of these endocardial "pseudocysts" remains uncertain The ulcerating carcinoma and terminal bronchopneumonia may represent remote portals of entry of invading organisms however the endocardial lesions may have begun as non bacterial vegetations which subsequently underwent secondary infection or ischemic necrosis or both There were however no lesions in any transitional stages of this process Furthermore non bacterial vegetations most commonly begin on the cardiac valves which was not true in this case The uniform stage of maturity of the "pseudocysts" suggests a single episodic event as the primary cause

Persaud and Milstoc and Berger[3] reported the only three similar cases of endocardial pseudocysts in the English literature The clinical background in their cases was one of chronic debilitating illness the lesions were identical both grossly and microscopically with those mentioned above In the two cases of Persaud, burns and bronchiectasis were present in one instance streptocci were cultured from the endocardial lesions and in the second case cytomegalovirus was observed both in the lesions but also in most organs of the body It would be impossible from a practical viewpoint to determine whether such organisms found in these lesions we e primary causes or only secondary invaders. The single case reported by Milstoc and Berger presented such endocardial lesions together with a myocardial abscess which may have been a primary cause or possibly a secondary complication of the few adjacent endocardial lesions.

A review of the limited case material suggests that this type of endocardial lesion develops in the presence of debilitating illness which is remote from rather than approximate to the heart and endocardium

The electrocardiographic changes in the present case suggest acute anteroseptal myocardial infarction though autopsy revealed only scattered microscopic areas of individual fiber necrosis and a few inflammatory cells in the myocardium. Recent studies suggest such foci of myocytolysis can be

years (mean 50 years) were divided into two groups the first group consisted of ten normal subjects (studied because of chest pain of uncertain etiology) and was considered as control the second group consisted of 22 patients having typical angina (with 75 per cent or greater luminal obstruction in at least one of the major coronary artery branches) All subjects underwent cardiac catheterization and coronary angiography

Production of lactic acid in the coronary sinus or extraction of less than 10 per cent was considered to be a sign of myocardial energy deficiency and of anaerobic glycolysis

In the first group only one patient showed production of lactate after ventricular angiography another one showed an extraction of less than 10 per cent

In the second group (CAD patients) all of them except one showed either less than 10 per cent extraction or production of lactate (Fig 1)

Atrial pacing (140 beats/minute × 10 minutes) performed in 12 patients of the CAD group resulted in marked lactate production only in seven patients whereas three patients showed a reduction of lactate and two patients showed no change

The increase of lactic acid production after left ventricular angiography does not show a correlation with either the degree of coronary occlusion (using Gensini s scores) or with ejection fraction or with variation of LVEDP

It seems likely that the perfusion of coronary capillary bed by contrast medium could be the determining factor in the onset of anaerobic metabolism

The practical interest of our observation is the availability of a reliable method to assess myocardial metabolism by a single routine procedure like left ventricular angiography

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Unusual cystic endocardial lesions

To the Editor

An unusual form of cystic endocardial lesion found in association with chronic debilitating illness may require special attention from echocardiographers especially as their instruments become more sensitive

An illustrative case was a 78 year-old white female who complained of shortness of breath and was found on hospital admission to have a right lower quadrant mass melena an iron deficiency anemia a white blood cell count of 38 000 and serial electrocardiograms compatible with acute anteroseptal myocardial infarction Chest x ray revealed only cardiac enlargement and bilateral pulmonary congestion Shortly after admission the patient developed hypotension increased pulmonary congestion oliguria and eventually coma she died on the third hospital day

At autopsy a fungating moderately well differentiated adenocarcinoma of the caecum approximately 7 cm in length was identified together with microscopic metastases to regional lymph nodes and liver Extensive pelvic thromboses were associated with recent embolism to the smaller pulmonary arteries

The heart weighed 340 grams and showed occlusive coronary atherosclerosis with microscopic foci of patchy fibrosis All valvular structures were normal On the left ventricular endocardium there were numerous discrete round and ovoid soft grayish yellow fluctuant masses 0 1 to 2 0 cm in diameter filling the recesses of the trabeculae carneae (Fig 1) These lesions were smooth globular soft easily compressible and



Fig 1 Endocardial pseudocysts with abscess formation confined to the areas of the trabeculae carneae of the left ventricle

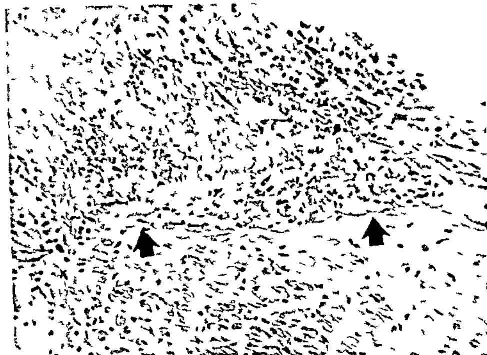


Fig 2 High power view of endocardial lesion showing acute inflammatory cells cellular debris necrotic material, fibrin and erythrocytes portion of normal myocardium *(lower right)* (Hematoxylin and eosin stain)

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The heart weighed 340 grams and showed occlusive coronary atherosclerosis with microscopic foci of patchy fibrosis All valvular structures were normal On the left ventricular endocardium there were numerous discrete round and ovoid soft grayish yellow fluctuant masses 0 1 to 2 0 cm in diameter filling the recesses of the trabeculae carneae (Fig 1) These lesions were smooth globular soft easily compressible and

3? other patients who had positive tests and *no* symptoms at all. That included pain or other kinds of anginal equivalents that were usual for that particular patient as determined by his history Unusual equivalents were excluded as best we could by questioning the patients While patients with angina *may* have the same pain pattern with each episode studies like ours (and those performed with Holter monitoring) question how consistent such a pattern is Finally the pain threshold factor should not be glibly dismissed by the observation that since all patients had a "chest pain syndrome the pain threshold could be simply discovered by historical features Because of psychological factors denial and subcultural norms influencing the kinds of symptoms that are most acceptable for patients to admit the relatively soft data that is obtained by history taking is not as valid for statistical analysis as is harder data such as th re ponse to Achilles tendon pain etc., as measured by some standardized test Since we did not do these more sophisticated tests we were not prepared to defend any conclusions regarding pain threshold based only on the kind of soft data cited

4 In his final paragraph Dr Liss apparently agrees with our conclusions, and he suggests that other noninvasive techniques may help unravel the problems of defective anginal warning systems This appears inconsistent since from the tone of his letter it would seem that if th patient had a positive exercise test associated with a radionuclide scan or any other noninvasive procedure Dr Liss would still question the adequacy of the history Was the patient a ked if there was a numb sensation between the third and fourth toes on his left foot? And so on ad nauseam From the point of view of clini al relevancy this is obviously not that pertinent Either one accepts the concept of a defective warning system whatever its etiology and however it is defined or one does not If one does accept it then the role of angina as a useful *warning* symptom needs to be re-emphasized to the patient The patient without angina or its equivalents during some or all ischemic episodes may require a much more cautious approach in regard to recommendations about stressful activities, physical training programs etc This is the impl cation of our study and we hope to have more data in this regard in future reports

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Retrograde Wenckebach effect in VT

To the Editor

I was interested to read the *Letter to the Editor* by Drs Cotoi, Georgescu and Cozlea, that appeared in the May 1978 issue of AMERICAN HEART JOURNAL— Retrograde Wenckebach phenomenon in ventricular tachycardia (95 6 6 1978)

In 1951 my associates and I reported this phenomenon clearly documented in a male physician with ventricular tachycardia of 57 days duration

Pordy L., Kolker J and Levy H Paroxysmal ventricular tachycardia of prolonged duration Analysis of retrograde Wenckebach effect by polygraphs and electrokymogram Review of present therapy Am J Med 10 254 1951

It was gratifying to learn of another manifestation of this phenomenon which we reported so many years ago

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Lenegre s disease in youth

To the Editor

We have read with interest the case report by Dianzumba and colleagues entitled Lenegre s disease in youth " describing a 22 year-old, apparently healthy man who presented *with symptomatic AV block We recently saw a 20-year old* otherwise healthy female who presented with intermittent

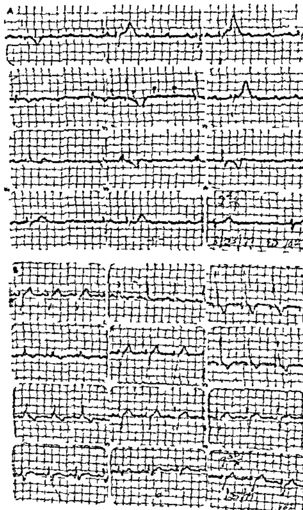


Fig 1 *Panel A* ECG on admission Sinus tachycardia 125 per minute with high degree AV block and intermittent complete AV block The ventricular rate is 31 per minute The QRS morphology suggests RBBB and left anterior fascicular block. *Panel B* ECG a few hours after admission The AV block has disappeared The QRS pattern now suggests RBBB and left posterior fascicular block

associated with ECG patterns of transmural infarction[3]

Since the endocardial lesions were not suspected during life in the present case no special diagnostic techniques were used Physicians who regularly interpret echocardiographic studies should be aware of this lesion and identification of such pseudocysts during life should prompt the physician to search for occult malignant disease and possibly for sites of chronic infection in the patient

The prognostic significance of these cystic endocardial lesions remains in doubt since to date they have been identified by autopsy only in a setting of other serious life threatening illness It is quite possible that such lesions may heal as the underlying illness improves all evidence of their previous existence may disappear during the healing process Identification of these lesions by echocardiographic technique during life might not necessarily imply a negative prognosis

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Silent or asymptomatic myocardial ischemia

To the Editor

I read with much interest the article in the April 1978 issue of AM HEART J entitled Silent myocardial ischemia during and after exercise testing in patients with coronary artery disease by Drs Lindsey and Cohn (AM HEART J 95 441 1978) I fail to understand how the authors can conclude from the data they presented in their article that there may be silent or asymptomatic myocardial ischemia just as there may be silent myocardial infarction Their initial statement that they studied the exercise responses of 232 consecutive patients with chest pain syndromes negates the word silent Only 122 of these 232 patients with coronary artery disease and an abnormal ECG response to exercise testing were reported upon Their two step test was considered positive if there were new or additional J point depression greater than 0 5 mm while exercise tests performed on a bicycle were required to have 0 1 mm ST segment depression

In their discussion Lindsey and Cohn state A majority of the patients in both groups had a history of angina that could be described as typical but this occurred as frequently and with the same severity in both subgroups Once again the word silent does not seem indicated In their conclusion they admit that three of the 44 pain free patients did have an anginal equivalent mainly dyspnea In regard to their third conclusion I fail to understand the comment We did not conduct pain threshold tests to determine if our pain free group actually had a higher than normal pain threshold This seems obviated by the fact that all patients had a chest pain syndrome The threshold could simply have been discovered by review of records and/or speaking to the patients involved Their fourth comment that their patients may have experi enced truly unusual anginal equivalents once again could have been discovered by the appropriate history It is well known that patients with angina pectoris or its equivalent often have the same response with each episode of coronary insufficiency

Although a considerable number of patients with coronary artery disease may have ECG evidence of exercise induced myocardial ischemia without angina or its usual equivalents I do not see how the authors can make this conclusion from their study I agree that there may be a group of non responders but their non response may be a result of inade quate history inadequate testing and failure to use the ancillary methods of exercise testing at our disposal

The use of systolic time intervals phonocardiograms echo cardiography radionuclide imaging and real time radionu clide cineangiography may help unravel the mystery of the defective warning system

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Reply

To the Editor

Several points in the letter from Dr Liss require clarifica tion

1 Dr Liss objects to our term silent because all of the patients had a chest pain syndrome and a majority of them had typical angina as well In our paper we specifically noted that silent referred to the absence of symptoms during a positive exercise test This was done in order to make the point that not all episodes of ischemia are associated with pain The analogy might be made to the individual who has had angina who has suffered an infarction with pain and then suffers one without pain or any of his other usual symptoms We would interpret that second infarction as being a silent one and believe that most cardiologists would agree

2 The 122 patients reported from our consecutive series were those who had positive tests and coronary artery disease as clearly stated in the text We did not discuss the other 48 patients in our series without heart disease who had positive or negative tests nor did we discuss the 62 patients with coronary disease who had negative tests Correlating the presence or absence of pain during a negative test in patients with coronary disease presents a difficult set of problems in defining an ischemic episode hence our decision to limit our discussion in the present report to those patients with clearly positive tests and angiographically determined coronary artery disease The criteria for positive tests that we used are the standard ones employed for the two types of tests and as noted similar numbers of both kinds of tests (two step test and bicycle) were performed in the subgroup with and without pain during positive tests thereby negating the methodology of the test as a discriminating factor

3 Three patients had dyspnea which was their usual anginal equivalent and nine others experienced fatigue which may or may not have been their usual anginal equivalent These patients were given special mention because there were

Book reviews

Congenital Malformations of the Heart and Great Vessels Synopsis of Pathology Embryology and Natural History By Hans Bankl Baltimore 1977 Urban & Schwarzenberg 264 pages.

The title of this book defines its contents very well The author is from the Faculty of Pathology of the University of Vienna Austria and the contents of this small but elegant book describe his own experiences and material from his department The book is divided into two parts one concerned primarily with embryology of the heart and the second with specific malformations. Although it contains nothing new the book summarizes concisely and extremely well in 264 pages the congenital anomalies of the heart and great vessels Readers will appreciate the book because of its brevity There are 793 references cited This book is worth owning by anyone who is concerned with cardiology

Angina Pectoris Edited by Desmond G Julian M D New York, 1977 Churchill Livingstone 272 pages Price $25 00

This is a useful and clinically oriented book on angina pectoris edited by Julian and written by 16 contributors The subject is concisely discussed including the history pathology pathophysiology diagnosis and medical and surgical management of angina pectoris Each chapter has appended a selected bibliography Angina pectoris is an important aspect of medicine and one of the most common diseases of man Every physician regardless of his specialty must contend with angina pectoris This is a very good up to-date review of the disease presented in a practical clinical manner for the average physician's benefit This is a highly recommended book for all practicing physicians especially general practicing physicians and internists

Chest Pain An Intergrated Diagnostic Approach Edited by Donald L Levene with Ronald F Billings Geoffrey M Davies John Edmeads, and Fredric G Saibil Philadelphia 1977 Lea & Febiger Publishers 203 pages Price $11 00

Chest pain is an interesting and important subject The editors and contributors discuss the neurological and psychological aspects of chest pain including pain arising from intrathoracic structures chest wall nerves and spinal cord extrathoracic structures, and emotional disorders A section is devoted to pain in children This paperback book of 203 pages is brief It can serve as a good review of chest pain for all physicians. Undergraduate medical students and housestaff should find this a source for rapid review of chest pain The book reminds physicians of the many causes of chest pain and the extreme importance of careful evaluation of pain in the chest A rapid and casual diagnosis can certainly lead to considerable errors in diagnosis expense to patients and mistreatment Chest pain is one of the most common complaints of patients. All of the eight contributors are from Toronto Canada The book is written for the practicing physician Some discussions are too brief and inadequate for example the presentation of the post cardiotomy syndrome on page 51 This is an extremely important and common syndrome which responds dramatically to proper therapy when administered early and responds relatively poorly when treated late The practicing physician should appreciate this book.

Second Henry Ford Hospital International Symposium on Cardiac Surgery Edited by Julio C Davila M D., New York 1977 Appleton Century Crofts Inc 732 pages Price $65 50

This symposium must have been an outstanding one to attend. The many participants were from various parts of the world and included surgeons presently engaged in cardiovascular surgery The subjects discussed are extremely interesting and the history of cardiac surgery which advanced so rapidly during the last 25 to 30 years is nicely described by those responsible for cardiac surgery Those who witnessed these advancements can appreciate this publication most and those who entered medicine recently certainly should read and enjoy this book

The book is divided into 17 sections all interesting each consisting of brief summaries of important aspects of cardiac surgery Among the sections are reflections on the development of cardiac surgery diagnosis extracorporeal circulation anesthesia congenital anomalies and surgery for them cardiac valve surgery and replacement myocardial revascularization management of pump failure and others The papers are relatively short but well written and clearly describe the authors contributions and thoughts The book is nicely printed and bound The illustrations are clear and the photographs interesting This publication is an excellent history of cardiac surgery for a 25 year period up to about 1975 This is a valuable publication of the proceedings of what must have been a very good and well organized symposium

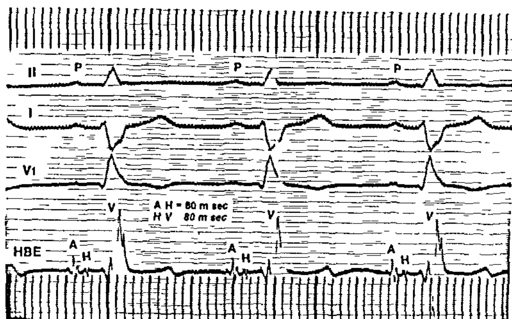


Fig 2 His bundle electrocardiogram *(HBE)* showing normal AH and prolonged HV intervals

symptomatic trifascicular block who conforms with the criteria for Lenegre s disease

Case report

The patient is a 20 year old apparently healthy female brought to the hospital because of recurrent episodes of dizziness of one week s duration The family history and past medical history were negative The physical examination on admission revealed peripheral pulse of 30 per minute and blood pressure of 170/90 mm Hg The rest of the examination *including the cardiovascular system was unremarkable* The initial electrocardiogram revealed sinus rhythm with atrial rate of 125 per minute high degree AV block and intermittent complete AV block The ventricular rate was 31 per minute The QRS complexes had a pattern of RBBB and left anterior fascicular block (Fig *1A*) A temporary transvenous pacemaker was inserted The chest x ray cardiac fluoroscopy echocardiogram and other laboratory data revealed no abnormalities The electrocardiographic monitoring in the CCU revealed intermittent nature of the AV block with symptoms appearing during the period of AV block On the sixth hospital day a permanent pacemaker was implanted The twelve lead ECG during normal AV conduction showed regular sinus rhythm 80 *per minute PR interval 1 6 second RBBB and left posterior* hemiblock (Fig *1B*) A His bundle electrocardiogram during this time showed normal A H and prolonged H V intervals (Fig 2) indicating infranodal conduction delay Eight months after admission the patient now has returned to normal activity without symptoms The standard ECG after pace*maker suppression with chest wall stimulation shows persist*ing RBBB left posterior hemiblock and intermittent high degree AV block

The clinical and electrocardiographic data along with alteration in His bundle ECG suggest the etiology as Lenegre s disease To our knowledge this case represents the youngest patient with documented heart block possibly secondary to *Lenegre s disease*

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REFERENCE

1 Dianzumba S B Singer D H Meyers S Barresi V Belic N and Smith J M Lenegre s disease in youth Am Heart J 94 479 1977

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1979 Pediatric Cardiology Examination

The Sub Board of Pediatric Cardiology of the American Board of Pediatrics will offer its next written examination on Friday July 13 1979 To sit for the examination the following criteria must be met (1) Certification by the American Board of Pediatrics (2) Two years of full time graduate training in an approved pediatric cardiology program (3) Letters of recommendation from individuals able to attest to the applicant s fellowship training Candidates who achieve a qualifying score on the written examination will be eligible for the oral examination The oral portion of the examination will be held in October 1979 in San Francisco A candidate must be successful on both the written and oral portions of the examination in order to be certified

The registration period for the examination will extend from October 1 1978 to January 31 1979 Please contact the American Board of Pediatrics to receive an application for the examination The application fee for the written portion of the examination is $300 ($150 registration and $150 examination) An additional fee of $150 will be payable upon receipt of an appointment for the oral portion of the examination Direct inquiries to American Board of Pediatrics Suite 402 NCNB Plaza 136 E Rosemary St Chapel Hill N C 27514 Telephone (919) 929 0461

Third Symposium on Echocardiology

The Third Symposium on Echocardiology will be held at the Erasmus University Rotterdam The Netherlands on June 20 through 22 1979 The main program will consist of lectures by invited speakers selected contributions and a poster session A commercial and scientific exhibition will be held in conjunction with the meeting For registration information or further details please write 3rd Symposium on Echocardiology Thoraxcenter EE 2302 A P O Box 1738 3000 DR Rotterdam The Netherlands Attn Mr C T Lancée

Florence International Meeting on Myocardial Infarction

An International Meeting on topics related to myocardial infarction will be held in Florence Italy from May 8 through 11 1979 The meeting will be divided into a series of lectures given by invited speakers and a sharing of original communications by participants Communications selected by the Scientific Committee will be published together with the lectures in a volume issued by Excerpta Medica Amsterdam in 1979 For information regarding this meeting, please write Florence International Meeting on Myocardial Infarction Organizing and Scientific Secretariat Istituto di Patologia Medica II dell Università di Firenze Viale Morgagni 85 Firenze Italy Tel (055) 43 27 58

Sexuality and the Cardiovascular Patient

A two day national course entitled Sexuality and the Cardiovascular Patient will be conducted in Baltimore Md on April 27 and 28 1979 The course will be co sponsored by the American Heart Association Council on Clinical Cardiology American Heart Association—Maryland Affiliate Inc and the American Heart Association—Central Maryland Chapter Inc The purpose of the course will be to present to physicians cardiovascular nursing specialists and other allied health professionals the currently available information on the psychological and physiological aspects of sexuality of the various types of cardiovascular patients and the impact of this knowledge on cardiovascular rehabilitation For further information regarding this course please contact Michaeline R Silverstein Program Director American Heart Association—Central Maryland Chapter P O Box 17025 Baltimore M D 21203

Symposium on Infarct Size

A symposium on Infarct Size organized by Dr D Durrer of Amsterdam and by Dr F L Meijler of Utrecht will be held in Utrecht The Netherlands on April 9 and 10 1979 Topics will include Fundamental and diagnostic aspects of myocardial ischemia Arrhythmias in ischemia and infarction Pump failure and infarct size and Reduction of infarct size Deadline for registration is February 1 1979 Registration fee is 150 Dutch florins which includes luncheons For further information contact Dr Frits L Meijler Department of Cardiology University Hospital 3500 CG Utrecht The Netherlands

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